PREDICTION OF PRE-OPERATIVE LOCAL STAGING AND OPTIMISING TREATMENT RESPONSE TO NEOADJUVANT THERAPY IN COLORECTAL CANCER.

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ABSTRACT

The presence of abnormal Lymph Nodes (LNs) in patients with colorectal cancer is an essential determinant of prognosis and guides treatment options (surgical and medical). Staging with Computed Tomography (CT) is somewhat inaccurate in determining true nodal status. As a result, either approximate estimates must be made on imaging, or definitive nodal staging determined by surgical resection before recommendations about the risk vs benefit of chemotherapy can be made reliably.

Patients with advanced rectal cancer are commonly referred for neoadjuvant therapy as part of standard care treatment protocols based on Magnetic Resonance Imaging (MRI) local staging. Following neoadjuvant therapy, many patients then undergo surgical resection. However, a significant proportion achieve a complete Clinical Response (cCR) with modern neoadjuvant treatment, and these patients are increasingly offered non-operative management and surveillance with the goal of organ preservation. Accurate clinical staging parameters and predictive markers of tumour response may help guide more personalised treatment strategies and identify potential candidates for non-operative management more accurately.

Within the past decade, a promising new strategy termed Total Neoadjuvant Therapy (TNT) has been shown to improve compliance with chemotherapy, by delivering this sequentially with chemoradiotherapy prior to surgery in patients with rectal cancer. TNT has the potential to reduce distant failure risk and provide significantly higher rates of pathological Complete Response (pCR) and cCR with an opportunity to manage patients non-operatively, however, optimal treatment sequencing of radiotherapy and chemotherapy remains somewhat unclear.

Pre-operative prediction of nodal status in colon cancer, neoadjuvant treatment response in rectal cancer, as well as optimal sequencing of neoadjuvant therapy, represent major areas of weakness in current treatment paradigms in colorectal surgical oncology. Furthermore, they are all areas of active research, and frequently tie in together during Multi-Disciplinary Team meeting (MDT) discussions in clinical practice.

The aims of this thesis are: Firstly, to investigate Artificial Intelligence (AI) models for prediction of LN status on preoperative staging CT in patients with colon cancer. Secondly, to identify pre-treatment factors predictive of Complete Response (CR) following neoadjuvant therapy in patients with Locally Advanced Rectal Cancer (LARC), specifically sarcopenia, clinical and biochemical factors. Lastly, to determine whether a Personalised Total Neoadjuvant Therapy (pTNT) protocol with sequencing tailored to the clinical stage at presentation results in better short-term oncological outcomes compared to a uniform protocol for all patients with advanced rectal cancer.

To achieve these aims, two meta-analyses were performed to identify the gaps in the field of AI LN detection. The first, focused on the accuracy of deep learning algorithms and radiomics models compared with radiologist assessment in the diagnosis of lymphadenopathy in patients with abdominopelvic malignancies and the second solely focused on colorectal cancer. Subsequently, a deep learning model was developed to assess LN status on staging CT in patients with colon cancer, and the model's performance was compared with baseline results of a prospective study evaluating the accuracy of preoperative staging.

A systemic review and meta-analysis were performed to identify and assess AI segmentation models able to predict sarcopenia using CT scans. Following this, an institutional colorectal cancer database was interrogated to determine if sarcopenia or clinical and biochemical markers were associated with tumour response in patients with LARC.

Prospective data was collected on patients in two hospitals who underwent pTNT based on their clinical staging at presentation for the treatment of advanced rectal cancer. A cohort study was performed to summarise tumour response, chemotherapy compliance and the toxicity profile of patients. An additional multicentre retrospective cohort analysis comparing pTNT over a 3-year period to a historical cohort of randomised control trial patients who had extended chemotherapy in the wait period (xCRT) or standard long course Chemoradiotherapy (sCRT) was conducted.

The two meta-analyses determined that deep learning assessment of LNs demonstrated the greatest potential for assessment of LN without the need for surgery, with MRI for rectal cancer and CT in colon cancer providing the greatest accuracy. Our clinical studies demonstrated that radiological assessment remains the most effective preoperative method of staging LNs, with histology considered the gold standard. Deep learning assessment using a ResNet-50 framework is limited to very low accuracy and specificity in detecting abnormal LNs when compared to the radiologist's assessment. It is likely that the poor performance of the deep learning model is attributed to the lack of features extracted from the CT scans.

The meta-analysis found that deep learning segmentation models can accurately predict sarcopenia using CT scans. However, sarcopenia was not found to be a predictor of pCR in patients with LARC. The clinical predictors of good tumour response after neoadjuvant therapy for rectal cancer were found to be a clinical T2 stage and Body Mass Index (BMI) $\geq 25 kg/m^2$. Pre-treatment biochemical markers were not predictive of tumour response after neoadjuvant therapy for rectal cancer.

Our research found that over 40% of the patients who underwent pTNT for the treatment of advanced rectal cancer demonstrated a complete response in the primary tumour (pCR and/or cCR)

resulting in a high rate of organ preservation. Furthermore, 45% of the patients with stage M1 disease achieved a complete M1 response. Compliance with chemotherapy was over 95% and toxicity was lower than expected. When comparing a pTNT approach with xCRT or sCRT in patients with LARC, there was a significant difference in complete response and cCR rate favouring the pTNT group compared to the xCRT and sCRT groups.

In conclusion, these results suggest that a deep learning model with a ResNet-50 framework does not serve as a reliable staging tool for the prediction of LN status using preoperative staging CT in patients with colon cancer. Despite a large volume of research, the ability to predict which patients are likely to achieve a complete response by measuring pre-treatment sarcopenia, clinical and biochemical markers remains elusive. Early results of a pTNT approach tailoring sequencing of neoadjuvant chemotherapy to disease risk at presentation are encouraging and compare favourably to xCRT and sCRT in patients with advanced rectal cancer.

STATEMENT OF DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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To my wife Danielle Bedrikovetski and son Kayden whose love and endless sacrifice gave me the strength to keep going. Thank you for enduring this process.

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Original Research

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Other publications related to the thesis

Glaser, S., Maicas Suso, G., **Bedrikovetski, S**., Sammour, T., & Carneiro, G. (2020). Semi-supervised multi-domain multi-task training for metastatic colon lymph node diagnosis from abdominal CT. In Proceedings of the IEEE 17th International Symposium on Biomedical Imaging (ISBI 2020) Vol. 2020-April (pp. 1478-1481). Iowa City, Iowa, USA: IEEE.

LIST OF ABSTRACTS AND PRESENTATIONS

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Bedrikovetski S, Dudi-Venkata N, Maicas G, Kroon HM, Seow W, Cairneiro G, Moore JW, Sammour T. Artificial intelligence for the diagnosis of lymph node metastases in patients with abdominopelvic malignancy: a systematic review and meta-analysis. Royal Australasian College of Surgeons 2021 Annual Scientific Congress, Melbourne, Australia (Oral presentation).

Bedrikovetski S, Dudi-Venkata N, Maicas G, Kroon HM, Seow W, Cairneiro G, Moore JW, Sammour T. Artificial intelligence for the diagnosis of lymph node metastases in patients with abdominopelvic malignancy: a systematic review and meta-analysis. European Society of Surgical Oncology 2020 Conference (Oral presentation).

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Bedrikovetski S, Dudi-Venkata N, Kroon HM, Traeger L, Seow W, Vather R, Moore JW, Sammour T. A prospective study of diagnostic accuracy of multidisciplinary team and radiology reporting of pre-operative colorectal cancer local staging. Tripartite Colorectal Meeting 2022, Auckland, New Zealand (Poster Presentation).

Bedrikovetski S, Traeger L, Fitzsimmons T, Vather R, Moore JW, Sammour T. Total Neoadjuvant Therapy vs chemotherapy during the 'wait period' vs standard chemoradiotherapy for locally advanced rectal cancer. Tripartite Colorectal Meeting 2022, Auckland, New Zealand (Poster Presentation).

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ABBREVIATIONS

Symbols

%	Percentage
I2	Inconsistency (Index of Heterogeneity)
GY	Gray
k	Cohen’s Kappa
kw	Weighted Kappa

A

AI	Artificial Intelligence
APR	Abdominoperineal Resection
ASA	American Society of Anaesthesia
AUROC	Area Under the Receiver Operating Characteristic Curve
AUC	Area Under the Receiver Operating Characteristic Curve
AJCC	American Joint Committee on Cancer
ANOVA	Analysis of Variance

B

BMI	Body Mass Index

C

CR	Complete Response
cCR	Clinical Complete Response
CEA	Carcinoembryonic antigen
CALHN	Central Adelaide Local Health Network
CI	Confidence Interval

CD	Clavien-Dindo
CNN	Convolutional Neural Network
CT	Computed Tomography
CRC	Colorectal Cancer
CRS	Colorectal Surgery
CSSANZ	Colorectal Surgical Society of Australia and New Zealand
CV	Cross-validation
CLOS	Classification based on Level of Suspicion
CRM	Circumferential Resection Margin
CLAIM	Checklist for Artificial Intelligence in Medical Imaging
CAPOX	Capecitabine and Oxaliplatin

D

d	Days
DNA	Deoxyribonucleic acid
DFS	Disease-free Survival
DSC	Sørensen–Dice Similarity Coefficient
DRM	Distal Resection Margin

E

eGFR	Estimated Glomerular Filtration Rate
ERUS	Endorectal Ultrasound
EMVI	Extramural Vascular Invasion
ECOG	Eastern Cooperative Oncology Group Performance Status

F

5-FU	5-Fluorouracil

FP	False Positive
FN	False Negative

G

GI	Gastrointestinal

H

HAR	High Anterior Resection
HREC	Human Research Ethics Committee

I

IV	Intravenous

J

JSC	Jaccard Similarity Coefficient

L

LARC	Locally Advanced Rectal Cancer
LAR	Low Anterior Resection
LASSO	Least Absolute Shrinkage and Selection Operator
LOS	Length of Stay or Length of Hospital Stay
LN	Lymph Node
LPLN	Lateral Pelvic Lymph Node
LV	Lumbar Vertebra
LDH	Lactate Dehydrogenase

M

Min	Minutes

MRI	Magnetic Resonance Imaging
MDT	Multidisciplinary Team Meeting
mFOLFOX6	5-Fluorouracil, Leucovorin, and Oxaliplatin

N

N	Condition Negative
nCRT	Long Course Neoadjuvant Chemoradiotherapy
NOM	Non-operative management
NPV	Negative Predictive Value

O

OR	Odds Ratio
OS	Overall Survival
oCR	Overall Complete Response

P

P	Condition Positive
pCR	Pathological Complete Response
PET	Positron Emission Tomography
pTNT	Personalised Total Neoadjuvant Therapy
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PACS	Picture Archiving and Communication System

Q

QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies

R

RAH	Royal Adelaide Hospital
RT	Radiotherapy
RCT	Randomised Controlled Trial
ResNet	Residual Network
RISRAS	Radiation-Induced Skin Reaction Assessment Scale

S

SD	Standard Deviation
SE	Standard Error
SM	Skeletal Muscle
SAT	Subcutaneous Adipose Tissue
SVM	Support Vector Machine
SWE	Shear-wave Elastography
SCRT	Short Course Radiotherapy
sCRT	Standard Chemoradiotherapy
STAT	Skin Toxicity Assessment Tool
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
STARD	Standards for Reporting of Diagnostic Accuracy

T

TNT	Total Neoadjuvant Therapy
TME	Total Mesorectal Excision
TNM	Tumour Node Metastasis

T test	Students T test
TP	True Positive
TN	True Negative
TRG	Tumour Regression Grade
TPA	Total Psoas Area
TPAI	Total Psoas Area Index

U

ULAR	Ultra-low Anterior Resection
US	United States

V

VAT	Visceral Adipose Tissue

W

WCC	White Cell Count

X

xCRT	Extended Chemoradiotherapy

CHAPTER 1: INTRODUCTION

1.1 Colorectal cancer

Colorectal Cancer (CRC) is the second leading cause of cancer mortality worldwide, accounting for an estimated 935,000 deaths annually. It is also the third most diagnosed cancer globally, with 1.9 million cases in 2020.[1] Over the past two decades, CRC incidence in Australia has progressively increased and as a result, prevention and new treatment programs for CRC are actively being evaluated and implemented.[2]

1.2 Abdominal and pelvic lymph nodes

Lymph Nodes (LNs) play a critical role in the human immune system by filtering the blood for pathogens and abnormal cells (blood-lymph loop). This also makes LNs a location for neoplastic cells to reside/accumulate.[3] The tumour cells enter lymphatic vessels and travel to the LNs along lymphatic drainage pathways, which often accompany the arteries supplying or veins draining a primary organ. The presence of local lymphadenopathy in patients with colorectal cancer is an essential determinant of prognosis and guides treatment options (surgical and medical).[4] The most common nodal groups involved are the mesenteric and mesorectal groups which can extend to the retroperitoneal and pelvic sidewall compartments.[5]

Metastases to LNs generally follow the nodal stations in a stepwise direction as seen in Figure 1.[6] The primary tumour cells travel to nodal stations that are closest to the primary tumour and then progress farther away but within the lymphatic circulation.[7] Metastases to a nodal station farther from the primary tumour without involving the nodal station close to the primary tumour (skip metastases) are infrequent, although haematogenous spread to distant organs like the liver and the lung is more common.[8]

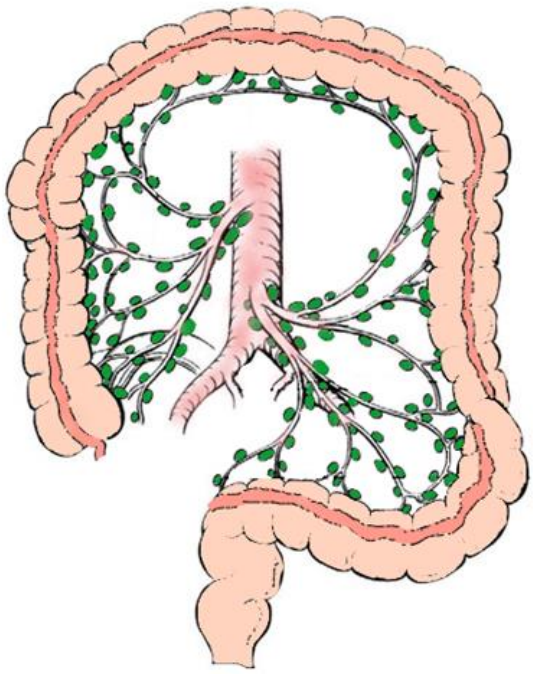

Figure. 1 Organisation of lymph nodes in the colon and rectum. Lymph nodes (coloured in green) surround the vasculature (coloured in red).

1.3 Imaging a patient with a diagnosis of CRC

Initial colon cancer staging investigations involve a contrast-enhanced Computed Tomography (CT) of the chest, abdomen and pelvis with intravenous and oral contrast.[9] A radiologist reports the details of this scan including; the location, size and extent of the primary lesion, invasion of adjacent structures, tumour factors that may affect the operation, visceral and peritoneal metastases and locoregional LNs (pericolic and local drainage) as well as metastatic LNs (mesenteric, retroperitoneal, pelvic and inguinal).[10]

In patients with colon cancer treated with curative intent, post-surgical resection LNs are inspected for metastasis by specialist pathologists allowing further decisions about adjuvant therapy. This is due to the inaccuracy of preoperative LN staging on cross sectional imaging (~70% accuracy) based on published prospective data.[11,12] In addition, the process of assessing every individual LN on a CT scan is time consuming and becomes an expensive process due to salary costs. As a result, LNs are

typically commented on incidentally on radiology reports and in multidisciplinary team meetings. Unlike in rectal cancer, LN status on preoperative imaging is not typically used to determine neoadjuvant treatment in patients with colon cancer. In rectal cancer the presence of abnormal local mesorectal or adjacent iliac lymphadenopathy is assessed preoperatively using high resolution Magnetic Resonance Imaging (MRI).[13] Pelvic MRI is somewhat more accurate than abdominal CT in determining nodal status, but rectal cancer anatomy is also somewhat distinct from colon cancer with other important local staging parameters such as circumferential margins used to determine requirement for neoadjuvant therapy.[14]

1.4 Neoadjuvant and Adjuvant Therapy

Patients with a new diagnosis of CRC are stratified into different treatment pathways, based upon preoperative tumour location and radiological staging after each case is discussed at a Multidisciplinary Team Meeting (MDT). The use of preoperative neoadjuvant therapy is not generally recommended in patients with stage I - III colon adenocarcinoma. Presently, the optimal treatment strategy remains surgical resection.[15] Following surgery, LN status on pathological assessment is used in determining if adjuvant chemotherapy is recommended (stage III and high-risk stage II patients). The FOxTROT trial investigated the potential efficacy of neoadjuvant chemotherapy administered to colon cancer patients with metastatic LNs.[16] The results presented at the 2019 American Society of Clinical Oncology Annual Meeting showed no significant difference in 2-year failure rate (defined as either relapse or persistent disease). There was, however, a significant reduction in incomplete tumour resection (R1 or R2) and pathological staging.[17] Although final results of this trial are yet to be published, preliminary data demonstrate that accurate preoperative detection of metastatic LNs may become a more factor in the treatment of colon cancer patients in future.

In contrast to colon cancer, neoadjuvant therapy is recommended for patients with newly diagnosed rectal adenocarcinoma with locally advanced clinical stage T3 or T4, and/or LN positive disease, Extramural Vascular Invasion (EMVI) or threatened Circumferential Resection Margin (CRM) on preoperative pelvic MRI.[18] Neoadjuvant Chemoradiotherapy (nCRT) followed by Total Mesorectal Excision (TME) and adjuvant chemotherapy is the accepted standard of care. Neoadjuvant therapy may consist of either Short Course Radiotherapy (SCRT; 25GY radiation over 5 days) or long course nCRT (variation around 50 Gy radiation over 5 weeks combined with 5 Fluorouracil [5-FU] based chemotherapy).[19] Radiotherapy plays a significant role in downstaging or downsizing rectal tumours in the neoadjuvant setting, resulting in a lower rates of local recurrence after surgery.[20] Following the completion of nCRT, patients traditionally undergo curative TME surgery 6-12 weeks later, irrespective of treatment response.[21] The goal of colorectal cancer surgery is en-bloc resection of the tumour, major vascular pedicles and the draining LNs with the aim of reducing local and distant recurrence rates.[22] However, surgery also exposes patients increased morbidity and mortality, as well as specific risks including but not limited to; anastomotic leak, the potential for a permanent stoma and impairment of bowel, bladder and sexual function.[23-25]

Approximately 15-20% of patients undergoing nCRT, develop a pathological Complete Response (pCR) defined as complete regression with an absence of residual cancer cells in both the primary tumour and mesorectal nodes.[19,26] However, not every patient responds well to radiation. Treatment-related toxicity can also occur, which often negatively impacts patients' overall health and quality of life.[27] Additionally, neoadjuvant radiotherapy can cause excessive tissue oedema and fibrosis that can compromise surgical planes, posing a significant surgical challenge especially in the narrow male pelvis.[28]

In the adjuvant setting, commonly prescribed chemotherapy agents for both colon and rectal cancer include 5-FU and Oxaliplatin.[29] These agents act to restrict tumour cell division. 5-FU prevents the

formation of essential nucleosides,[30] and Oxaliplatin acts via the formation of Deoxyribonucleic Acid (DNA) platinum adducts which deprive tumour cells of the essential building blocks for cell replication.[19,31] The goal of adjuvant therapy is to eradicate systemic micro-metastatic disease.[32]

With respect to rectal cancer, neoadjuvant therapy and surgical technique have improved oncological outcomes, reducing 5-year local recurrence rates to 5-10 per cent over the last 20 years.[33,34] However, the risk of distant relapse remains high at 30% in 10 years and is the leading cause of mortality in rectal cancer patients.[35] This is attributed to the lack of adjuvant chemotherapy compliance. More than half of eligible patients do not receive their full adjuvant chemotherapy due to delay in treatment, compliance issues, and postoperative complications.[36] As a result, research efforts have focussed on ways to improve the delivery of chemotherapy by administering the chemotherapy in the preoperative period. Total Neoadjuvant Therapy (TNT) for rectal cancer has been developed as a result, whereby all systemic therapy is delivered before surgery to address the limitations of adjuvant treatment.[37]

1.5 Cost related to Neoadjuvant therapy

Treatment recommendations differ between colon and rectal cancers, as well as by disease stage, resulting in different cost estimates.[38] Most recent Australian data shows the cost of early-stage disease has not substantially changed over time with costs ranging from AUD$34,337-AUD$43,776 per patient, as surgery alone is the main expense involved in treatment. However, neoadjuvant and adjuvant therapy for advanced disease is expensive. For example, the addition of Oxaliplatin, which is now standard of care for advanced colorectal cancer has significantly driven up costs to AUD$71,156 per patient.[39] Recent data from the US has shown cost-effectiveness for TNT at US$40,708 per life-year, versus USD$44,248 per life-year for conventional therapy.[40] This is largely because TNT can result in a clinical Complete Response (cCR), with patients avoiding surgery entirely. Recently the results of the OPRA randomised phase II trial assessed the outcomes of 324

patients with Locally Advanced Rectal Cancer (LARC) treated with TNT. The trial concluded that organ preservation was achievable in half of the patients with LARC treated with TNT. In turn, patients with a cCR would save the cost of TME, approximately USD$11,800.[41,42] This data and recent trends suggest that the treatment of later stages of colorectal cancer will involve more therapy being administered preoperatively in the neoadjuvant rather than adjuvant setting. However, this approach is fundamentally reliant on accurate LN staging to enable optimal targeting of neoadjuvant therapy.

1.6 Artificial Intelligence in Medical Imaging and its application to CRC

The number of patient scans performed and the ability to store them digitally has been steadily increasing over time. Artificial Intelligence (AI) has gained significant interest in the medical imaging field due to continual improvement in all aspects of image interpretation from detection, classification and automated image segmentation, to extraction of radiomic features and biomarkers.[43] AI in health care offers a substantial opportunity to improve patient outcomes while improving system efficiencies and reducing costs.[44] Human cognitive capability to effectively manage large sets of information is limited, and AI is likely to have an important and complementary role in this regard.

AI, machine learning, radiomics and deep learning are terms commonly used interchangeably despite being distinctly defined and this can create some misunderstanding in the field. AI encompasses deep learning and radiomics which are both subsets of machine learning that aid in pattern recognition for different data types (Figure 2).[45,46] Machine learning models are grouped into either supervised or unsupervised models. Supervised models rely on annotated data. The type of annotation depends on the task the model seeks to perform. In classification tasks where the focus is to identify the presence or absence of a disease, images are labelled in a binary fashion (disease positive or negative). For instance, in a study conducted by Glaser et al., a database

consisting of 123 CT scans of patients with colon cancer had each scan labelled as LN positive or LN negative.[47] As the exact location of the LN is not provided within the image, this is referred to as a weakly annotated database. Although the annotation does not specify the exact location of the LNs, the model might still automatically learn to predict if patients with colon cancer are LN positive or negative. The next level of annotation is drawing boundary boxes on each of the CT scans indicating the region of interest. This strategy is referred to as sparse annotation. The highest level of annotation is termed segmentation which consists of delineating or contouring the region of interest on each image. Segmenting the region of interest is a tedious and time-consuming process but it allows for more precise algorithms to be built. Alternatively, unsupervised machine learning models do not involve manual annotations and are used for clustering where the aim is to group data into homogeneous subgroups (e.g., identifying different CRC phenotypes). More recently, semi-supervised methods have been developed that combine annotated and non-annotated data together. A typical example of semi-supervised learning is reinforcement learning, in which the AI model gradually learns through better exploration of non-annotated data.[48,49]

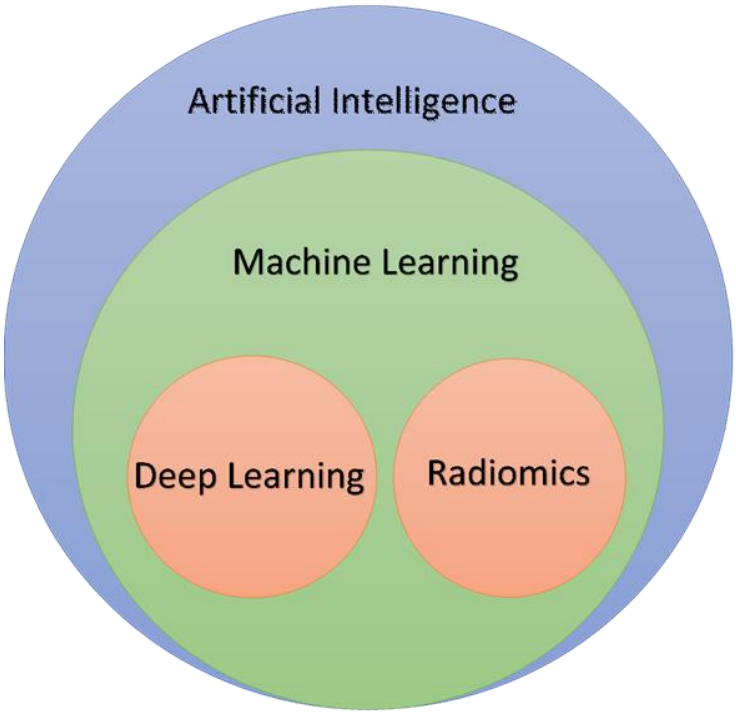

Figure. 2 Diagram illustrating subdivisions of artificial intelligence.

Radiomics is a field of research that relies on traditional machine learning methods, with some recent developments expanding further into deep learning methods. Radiomics can extract large amounts of data that are invisible to the human eye from medical images, uncovering advanced features that can characterise tumours and lymph nodes non-invasively through data analysis.[46] Radiomics can extract more complex features categorised as: morphological features (eg. shape, volume, diameter, image features), first order (eg. histogram, kurtosis, mean values, and textural features) or higher order features (eg. co-occurrence of patterns and filter response).[49] These features can be extracted from any imaging modality such as CT, Positron Emission Tomography (PET), or MRI. To choose the most prominent features according to the task, the algorithm will use different techniques such as random forest, least absolute shrinkage and selection operator (LASSO), support vector machine (SVM), logistic regression and others. It has been shown for the task of predicting lymphadenopathy, radiomics will create a unique phenotypic atlas for each tumour or LN and if paired with clinical data, this atlas enables the identification of new, reproducible, image-based biomarkers which have already been used to predict preoperative LN metastasis in patients with CRC.[50,51]

Deep learning refers to deep neural networks that do not necessarily require manually extracted features. The architecture is designed in a way that automatically recognises and extracts features, avoiding the need to manually define them (Figure 3). Deep learning models are composed of multiple layers where each layer learns a set of hidden features, which in most cases cannot be identified by a radiologist. The features in each layer are non-linear compositions of the features in the previous layer. This allows the model to first learn very simple features in the first layers, which are then merged to form more complex features for each layer.[52] In radiology, there are several architectures used to build deep learning models, one of which includes Convolutional Neural Networks (CNNs).[53] The main idea behind CNNs is the simple features in a small area of an image

can be analysed independently to their position and the rest of the image.[54] Hence, the image can be separated into small feature maps with each feature map being analysed in the same way and independently of the other feature maps. The information of each feature map can then be combined to generate a more abstract representation of the image. This relies on the succession of two different steps: convolution and sub-sampling. In a convolutional step a feed forward neural network (neural network where information moves unidirectionally) is applied to small regions of the image, creating several maps of hidden features.[54] In the sub-sampling step, the size of the feature map is reduced, this is done by transforming the neighbourhood of features to a single value. This reduction is accomplished by representing the neighbourhood of features with the maximum or the average value as a single value. These two steps are then merged into a deep network with several layers seen in the deep learning part of Figure 2. Deep learning models using CNN architectures have demonstrated excellent diagnostic performance in medical imaging detection of Alzheimer's disease, and breast and lung cancer.[55-57] In turn, with the success of CNNs, many other architectures have been introduced, including AlexNet, ResNet-50, ResNet-101, VGG16, and VGG19.[58,59] In particular, a ResNet architecture is shown to be used in recent studies to predict nodal staging on both radiological and pathological images from patients with CRC.[60,61]ResNet-50 as the name suggests is a 50-layer CNN, it consists of 1-maxpool layer, 1-average pool layer and 48 convolutional layers.[62,63] ResNet architecture makes use of residual blocks which in simpler terms are " identity shortcut connection" that skips one or more layers to improve the accuracy of the models.[64]

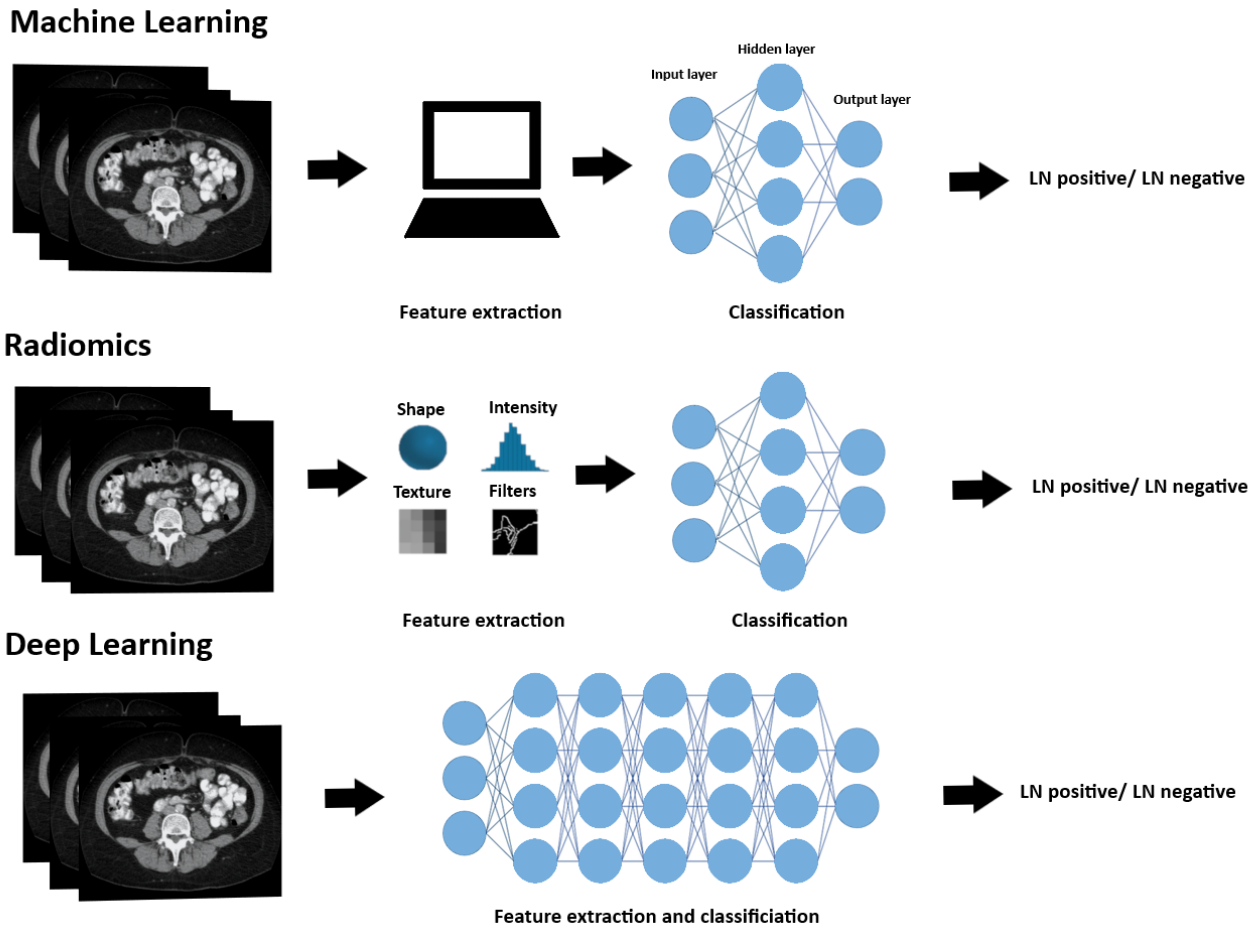

Figure. 3 Artificial Intelligence approaches. Differences between machine learning, radiomics and deep learning approaches for classification of LNs from abdominopelvic CT scans.

Developing an AI model successfully relies on the quality of the dataset on which it is trained, and it is often more important than the learning model itself.[65] This ensures that the model will perform equally well on unseen cases as it will on training cases. In radiology, AI models need to be generalisable to be used in multiple sites.[49] Thus it is important to have a dataset that represents the disease and different acquisition protocols.[66] A model for LN staging classification should be trained using a dataset reflecting the heterogeneity of lymphadenopathy patterns along with CT scans acquired from different scanner manufacturers. If the training dataset only contains a unique lymphadenopathy pattern (eg. All patients with colon cancer are node positive) or acquisitions are all performed using the same CT scanner, the model runs the risk of being poorly generalisable.

Datasets are usually divided into training, validation, and testing cohorts. During the training phase, the model's network is fed training data and tasked with making predictions at the output layer that match the known ground truth annotations, each component of the network produces an expedient representation of its input. Training a neural network means changing its parameters to optimise the outputs of the network.[66] Once the model has been trained, its performance is evaluated on the validation cohort. The model with the best performance in the validation cohort is further evaluated in the testing cohort.[49]

A recent report suggests that AI assisted diagnosis in areas such as cardiology, ophthalmology, pathology and oncology can potentially improve patient outcomes by 30-40%.[67] The financial benefits of AI are evident with estimates of up to USD $150 billion annual savings for the US health care system by 2026.[68] Considering the drastic improvements in patient outcomes and cost savings associated with AI, the only question remaining is which AI approach is most suitable for LN staging. Deep learning algorithms are typically better suited to handle data classification problems (i.e. lymph node being malignant or benign) with studies showing a substantial performance gain compared to traditional machine learning methods.[45,69] Despite the success of applying deep learning to medical imaging, currently, there is no evidence that deep learning can accurately predict LNs on preoperative staging CT in patients with colon cancer.

1.7 Predicting local response to neoadjuvant therapy in rectal cancer

The prediction of local response to nCRT in patients with LARC has been thoroughly discussed for many years. There have been excellent reviews published in 2015 and 2022 reassessing the current literature and highlighting the importance of this topic.[70,71] A number of parameters including clinical features such as the tumour stage according to the Tumour Node Metastasis (TNM) classification, tumour size and location within the rectum have been identified as predictors of

response to nCRT.[70,72,73] Moreover, several histopathological parameters were identified from tumour intrinsic features such as tumour budding and grade of tumour differentiation.[74,75] Lastly, biochemical factors have become increasingly attractive as predictors of local response to nCRT. Given the ease of blood sample collection and low cost, it would be convenient if these factors were found to reflect aspects of tumour biology. Despite the growing interest in predictors for local response to nCRT, no factors have yet reached clinical and external validation in large cohorts.

1.7.1 Clinical predictors of response to nCRT

Several clinical features have been identified as predictors of local response to nCRT in patients with LARC, including tumour size, tumour differentiation, clinical stage, and tumour distance from the anal verge.[73,76,77] Retrospective studies reported pre-treatment tumour diameter to be associated with treatment response in LARC. Bitterman et al. demonstrated that pre-treatment tumour diameter <3cm was an independent predictor of CR following nCRT in patients with locally unresectable T1-2 tumours and LARC.[78] Similar results have been shown in a larger population-based study showing that patients with tumour diameter <3cm are more likely to achieve a pCR after nCRT or SCRT regardless of their pre-treatment clinical stage.[79] There is recent evidence showing that pre-treatment tumour diameter is also a predictor of cCR in rectal cancer.[80] The authors also identified clinical Tumour stage (cT) to be associated with cCR, which has been a more comprehensive predictor of response.[80,81] Several studies comprising of large patient cohorts found a lower pCR rate in cT4 LARC and a higher cCR/pCR rate in patients with cT1-2 tumours after nCRT.[77,79,82,83] LN status was also found to be an independent predictor of local response.[72] Accordingly, patients with clinical node positive LARC were associated with significantly lower rates of pCR or cCR.[78]

Controversy remains between the association of tumour location and response to nCRT. In a retrospective study comprising of 173 patients with LARC, a distance from the anal verge of <5cm was significantly associated with pCR.[84] Similarly, a positive correlation of tumours located <3cm

from the anal verge with CR was also reported.[78] Conversely, Restivo et al, demonstrated that a distance from the anal verge of >5cm was a predictor of pCR in their cohort of 260 LARC patients.[85] Interestingly, a prospective study by Patel et al. found patients with low tumours (<4cm) and higher tumours (>8cm), were less likely to have a pCR.[86] Accordingly, exact reason for the association between the tumour distance from the anal verge and local response to nCRT remains undetermined.

Despite many studies reporting promising results, clinical predictors of local response to nCRT in LARC show poor sensitivity and specificity and have been contradicted in other studies.[76,87,88]

1.7.2 Biochemical predictors of response to nCRT

The correlation between local response of LARC to nCRT and biochemical markers in blood samples has been investigated. A Brazilian review has reported haemoglobin, Carcinoembryonic Antigen (CEA), C-Reactive Protein (CRP), White Cell Count (WCC), and several biochemical ratios as common predictors of pCR with consistency in the literature.[89] Higher level of preoperative haemoglobin were associated with higher rates of pCR and revealed a benefit in Overall Survival (OS).[90] CEA is well established as the recommended biomarker for CRC monitoring.[91] Patients who present with elevated CEA levels pre-nCRT are less likely to achieve a pCR.[92,93] Focussing on CRP, Aires et al. demonstrated low pre-nCRT CRP levels predicted a good response to treatment based on a cohort of 171 LARC patients. A multicentred Korean study showed that a reduction in pre-treatment WCC ratio during nCRT predicts good tumour response and is significantly associated with increased recurrence free survival.[94] Looking at further markers of inflammation, particularly relevant as a hallmark of cancer biology, an elevated pre-nCRT neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio are associated with lower rates of pCR and poor prognosis.[90,95-97] In addition, patients with a low pre-treatment lymphocyte-to-monocyte ratio had lower pCR rates and significantly worse disease free survival (DFS) and OS

after nCRT.[98,99] With regards to the smaller subgroup of patients that achieve complete response, recent evidence by Mbanu et al. revealed several clinical (pre-treatment tumour diameter, cT stage, total radiotherapy depths) and biochemical factors (haemoglobin, alkaline phosphate, neutrophil-to-lymphocyte ratio, neutrophil-monocyte to lymphocyte ration, lymphocyte count, albumin) associated with cCR.[80] Nevertheless, results vary between studies and very few have investigated a large number of biomarkers together.[100-102]

To date, no biochemical features have demonstrated an ability to predict local response with adequate sensitivity or specificity to reliably guide clinical practice. Given the limitations mentioned above, more studies including a variety of common pre-treatment biochemical factors are required to further explore the association between biochemical factors and the local response of patients with LARC to nCRT.

1.7.3 Sarcopenia

Sarcopenia is a disorder characterised by loss of skeletal muscle mass, leading to reduced strength and function.[103] While the prevalence of sarcopenia in healthy individuals increases with age, the rate of sarcopenia is further increased in patients with CRC, with incidence up to 60%.[104] General risk factors include age, gender, Body Mass Index (BMI), reduced level of physical activity, and the presence of chronic disease and comorbidities such as diabetes.[105] Causes of sarcopenia include physiological aging, skeletal muscle disuse, systemic inflammatory processes, endocrine changes, chronic alcohol consumption, malnutrition and insulin resistance.[106] While ageing naturally disturbs skeletal muscle integrity, changing the balance between hypertrophy and regeneration, sarcopenia is a multifactorial disorder that involves muscle changes attributed to both cellular and molecular pathways.[107] Acute and chronic diseases have detrimental effects on metabolism, speeding up catabolic processes, and there is growing interest in understanding the role of sarcopenia and its association with cancer and outcomes. Cancer patients commonly experience weight loss and

muscle degradation which can be exacerbated during treatment. Some evidence suggests that tumour mass in cancer patients is responsible for molecular dysregulation, ultimately resulting in muscle atrophy.[104,108]

The challenge in clinical practice is the lack of a quick and reliable measurement tool for sarcopenia, hence routine assessment is not typically performed in clinical practice. In the tertiary care setting, clinicians and surgeons commonly use the subjective "eye-ball end of the bed" test to diagnose sarcopenia. Contrast-enhanced CT scans are routinely conducted in the pre-treatment staging of patients with CRC, and medical image analysis is recognised as one method of quantifying skeletal muscle mass. Measurements taken at the third lumbar vertebra (L3) is validated as the standard for body composition. Estimates of skeletal muscle size at this level can provide a surrogate marker for sarcopenia using formulas accounting for patient height and gender.[109] However, these measurements are limited by inter-observer variability, fat infiltration resulting in overestimation of muscle mass, and practical considerations including time restrictions impacting health service efficiencies, limiting their use in practice (Figure 4).

The etiological factors of sarcopenia in cancer including systemic inflammatory processes, endocrine changes and dysregulation of cellular and molecular pathways are also observed in oncological treatment strategies.

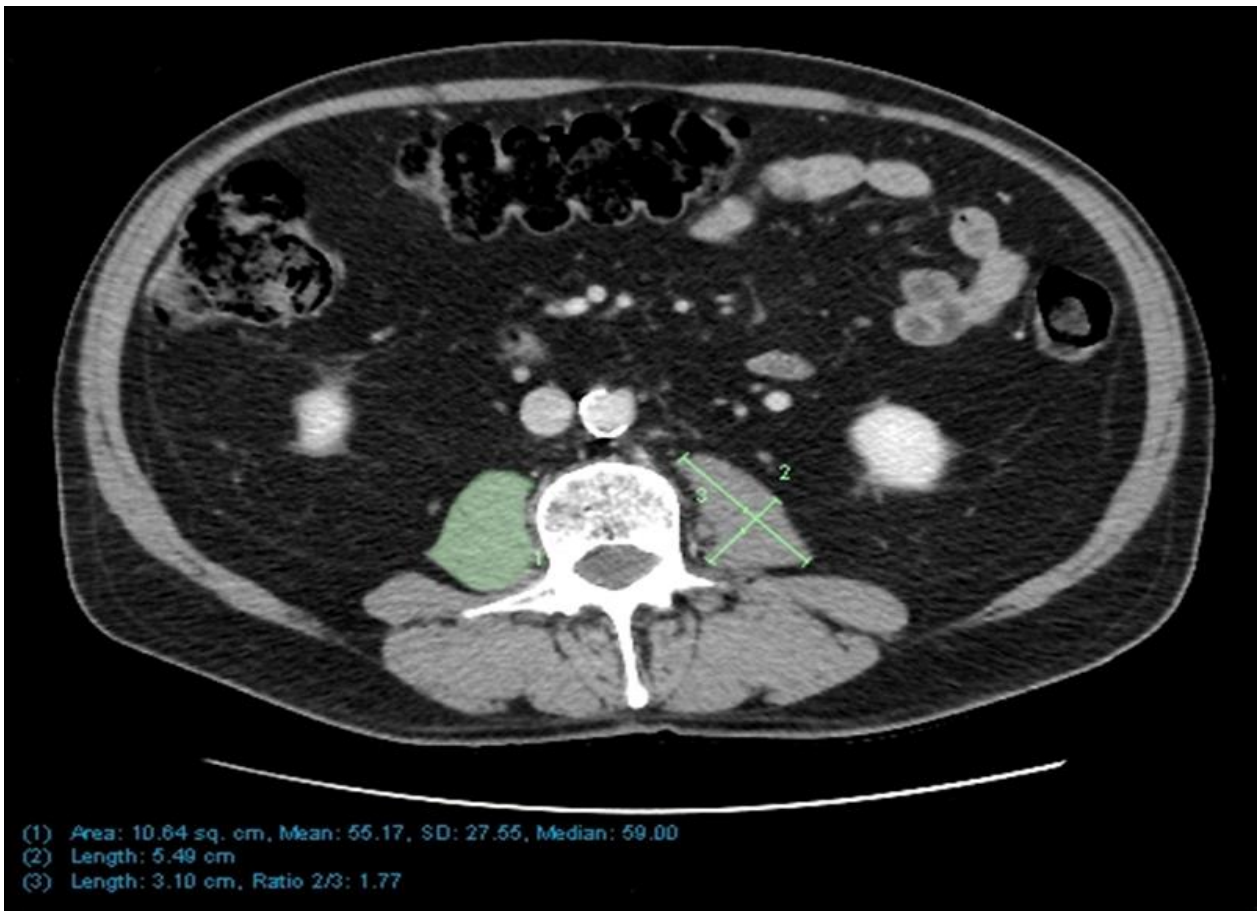

Figure. 4 Measurement of psoas muscle area in a CT image at the L3 vertebral body.

Cancer therapies such as surgery, chemotherapy and radiotherapy, often cause vomiting, loss of appetite, fatigue and pain, potentially leading to further muscle atrophy.[110] Sarcopenia increases susceptibility to chemotherapy toxicity among metastatic CRC patients.[111] Sarcopenic patients have a lower muscle mass compared to non-sarcopenic patients. The occurrence of chemotherapy overdose in sarcopenic CRC patients may potentially be due to the altered ratio between muscle mass and chemotherapy dosage. More importantly, since sarcopenia diagnosis is rarely considered in oncological treatment, necessary reductions in dose delivery are not identified and ultimately patients are treated inadequately.[112] The severity of adverse reactions and complications to oncological treatment strategies can impact hospital stay and readmissions, increasing the cost burden to the healthcare system and patient.[38,113]

Sarcopenia is known to have a negative association with not only chemotherapy toxicity but also postoperative complications, quality of life and overall survival.[114] Up to a third of patients suffer a postoperative complication following colorectal resection with rates of 17% in colon cancer and 30% for rectal cancer in Australia and New Zealand.[115] Sarcopenic CRC patients experience a significant increase in infection rates, increased inflammatory response, physical disability, delayed recovery and in those with advanced staging have worse DFS and OS.[108,116,117] Moreover, sarcopenia is reported to be associated with an increased risk of anastomotic leak, high grade complications (Clavien-Dindo Grade 3-4), longer hospital length of stay and higher hospitalisation costs.[108,109,118,119]

Sarcopenia places a substantial economic burden on the healthcare system.[120] The total estimated cost of hospitalisations in individuals with sarcopenia in the United States is US$40.4 billion with an average cost per person of US$260.[121] Recent evidence suggests that sarcopenic CRC patients have significantly higher total hospital related costs in comparison to non-sarcopenic patients.[122] Sarcopenia is associated with postoperative infection and longer hospital stay for CRC surgical resection (6.6 vs 5.4 days; P=0.03).[123] Patients experiencing other post-operative complications stay approximately 10 days longer and have over seven times the risk of in-hospital death than those without complications. The presence of an adverse event increases the cost of each admitted episode by AU$6,826 after adjusting for age and comorbidity.[124] The most recent Australian data indicates the total cost of adverse events was AU$460.3 million, representing 15.7% of the total expenditure on direct hospital costs, equating to an additional 18.6% of the total inpatient hospital budget.[115,124]

Although this would be biologically plausible, it is unclear whether there is any correlation between sarcopenia and tumour response to neoadjuvant treatment in rectal cancer. It would stand to reason

that because of increased susceptibility to treatment-related toxicity, tolerance to and compliance with treatment would be adversely affected, but this has not been formally investigated.

1.8 TNT for rectal cancer

Studies have highlighted potential drawbacks of adjuvant chemotherapy in patients with LARC and several ongoing clinical trials are assessing different therapeutic strategies to improve oncologic outcomes with nCRT. TNT is a promising new strategy that attempts to optimise the delivery of trimodal therapy with the incorporation of chemotherapy before or after nCRT or SCRT and prior to surgery. The two approaches are: (1) chemotherapy first (as induction therapy), followed by SCRT or nCRT then surgery and (2) SCRT or nCRT first followed by chemotherapy (as consolidation therapy), then surgery (Figure 5). The relative merit of these two schemas is an active area of investigation.[71]

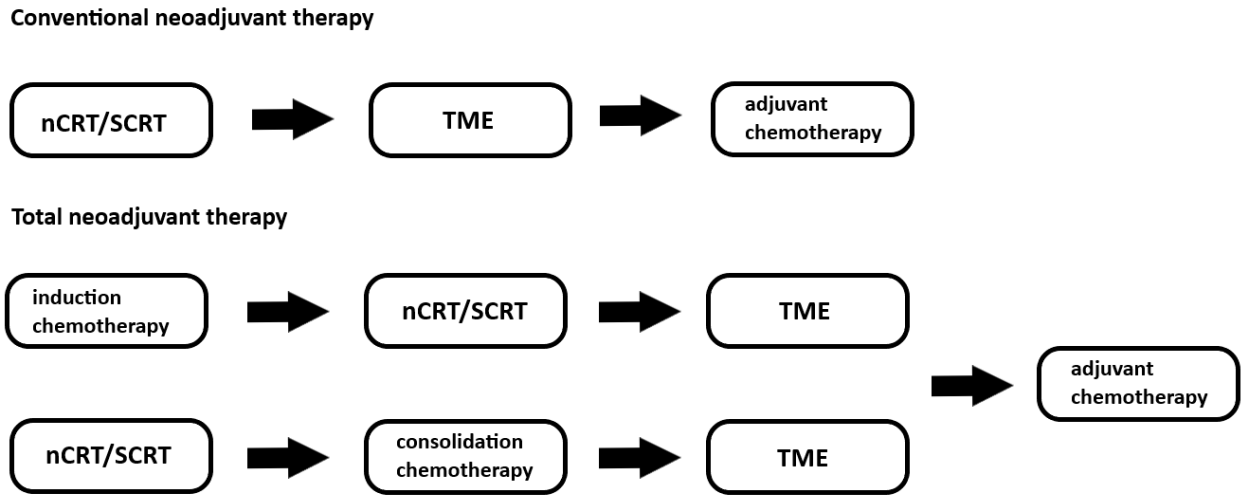

Figure. 5 Total Neoadjuvant Therapy.

The rationale behind the use of TNT is to improve compliance to treatment, enhance treatment tolerability, increase tumour downstaging, facilitate organ preservation through Non-Operative Management (NOM) in select patients, offer earlier treatment of micro-metastases to improve DFS

and decrease the interval from ileostomy to reversal.[125] There are some potential disadvantages to TNT which include delay to resection (potentiating tissue fibrosis which, in theory, can increase the surgical difficulty) and development of chemotherapy toxicity that may impact the possibility of definitive resection or lead to decline in performance and nutritional status. Due to inaccuracies in pre-operative staging, some patients may also be over-treated with this strategy.

The phase II TIMING trial investigated whether adding cycles of mFOLFOX6 between nCRT and surgery patients with LARC would increase the pCR rates in a four-arm design.[126] The pCR rate tended to significantly increase with the number of added chemotherapy cycles during the waiting period (P=0.004). The pCR rate was highest (38%) with the group who received 6 cycles of mFOLFOX6 and the longest interval to surgery (20 weeks) after nCRT and lowest (18%) in the group who received no cycles and had the shortest time to surgery after nCRT (6 weeks). Long-term data of the TIMING trial revealed that adding neoadjuvant consolidation chemotherapy after nCRT lead to increases in treatment compliance and DFS, however no significant change was observed in regard to OS or surgical complications (Clavien-Dindo graded ≥3).[127,128] The strategy of administering consolidation chemotherapy in the interval between SCRT and surgery to further increase rates of pCR has also been tested and compared with conventional nCRT in the POLISH II trial.[129] The trial included patients with poor prognosis such as cT3/4 tumours, with approximately half of these tumours located in the lower rectum. Trial results showed no significant difference in 7-year DFS and OS between the two groups.

More recently, the phase III RAPIDO trial compared SCRT followed by 18 weeks of consolidation chemotherapy then TME, to conventional nCRT and reported improved rates of pCR (28% vs 14%, P<0.0001) in addition to improved disease-related treatment failure (23.7% vs 30.4%, P=0.019) after a 4-year follow up.[130] There were no significant differences in the severity of adverse events between the two treatment arms (38% vs 34%). In the experimental arm, 85% of patients completed

neoadjuvant chemotherapy, although 37% of patients who started adjuvant therapy in the nCRT group prematurely stopped chemotherapy due to poor compliance. The phase III trial PRODIGE 23 investigated whether induction chemotherapy (mFOLFIRINOX) before nCRT followed by TME and adjuvant therapy improved DFS compared with conventional nCRT in patients with resectable non-metastatic LARC. The trial reported significantly higher pCR rates (11.7% vs 27.5%, P<0.001), 3-year DFS (68.5% vs 75.7%, P=0.034) and 3-year metastasis free survival (71.7% vs 78.8%, P<0.02) in the TNT arm without any difference in surgical complications in comparison with the conventional nCRT arm. However, neither the PRODIGE 23 nor RAPIDO trials have shown an OS advantage in the TNT arms.

In contrast, CAO/ARO/AIO-12 had TNT in both arms which consisted of 3 cycles over 6 weeks of induction or consolidation chemotherapy (FOLFOX) with nCRT. The consolidation arm achieved a higher pCR (25%) compared to the induction arm (17%). Notably, the radiotherapy related severe adverse event rate was lower and compliance was higher in the consolidation chemotherapy group with upfront radiation. Conversely, the chemotherapy induced severe adverse event rate was lower and compliance was higher in the induction chemotherapy group with upfront chemotherapy. This suggests that the treatment modality given first within TNT will have better compliance and lower toxicity rates and vice versa. Comparable to CAO/ARO/AIO-12 is the OPRA Trial which used 4 months of induction or consolidation FOLFOX or CAPOX chemotherapy with nCRT with a primary aim to detect a 10% improvement in DFS in either treatment arm compared to a 75% historical rate.[42] Patients who achieved a cCR or near-cCR were offered NOM and the remainder underwent surgery. Although OPRA reported no improvement in DFS in either group, they found a significantly higher 3-year organ preservation rate in the consolidation chemotherapy group compared to induction chemotherapy group (53% vs 41%, P<0.01). Unfortunately, the OPRA trial failed to report adverse events induced by nCRT and chemotherapy separately, however the authors

reported no difference in the overall rate of adverse events between treatment groups (41% vs 34%). In addition, while organ preservation was reported, rates of cCR were not.

Until now, most neoadjuvant treatment protocols have been designed for the "average patient" with LARC based on RCT inclusion criteria which reflect this. As a result of this "one-size-fits-all" approach, neoadjuvant treatments can be very successful for some patients but not for others. Personalised TNT (pTNT), one the other hand, is an innovative approach developed locally in South Australia that considers the patient's clinical stage at presentation to determine the sequence of preoperative chemotherapy (induction chemotherapy versus consolidation chemotherapy) before or after nCRT.[131] The hypothesis behind the pTNT approach for advanced rectal cancer is that patients with the need for systemic control should undergo induction chemotherapy to reduce the risk of distant failure and patients with the need for local control should undergo consolidation chemotherapy to reduce the risk of local relapse.[132-134] It is important to note, the lack of data throughout the literature supporting a personalised treatment approach over the standard of care treatment in patients with advanced rectal cancer.

1.9 Summary

Among the metastatic pathways of colon cancer, LN metastasis is the least well characterised pre-operatively owing to limitations in medical imaging and interpretation. LN metastases determine prognosis, and the potential benefit of neoadjuvant chemotherapy in select patients with colon cancer. To improve the performance of preoperative LN staging in colon, several image-based models have been proposed. Radiomics models derived from CT or MRI images are predominant, however deep learning seems to lead to a higher diagnostic accuracy. To date, no studies have attempted to use deep learning for predicting lymph node status on preoperative staging CT in patients with colon cancer.

At present the management of LARC includes nCRT followed by TME and adjuvant chemotherapy if indicated. nCRT results in downstaging in approximately two-thirds and cCR in one-fifth of patients. In the select group of patients that achieve a cCR, some authors have proposed advocating for organ preservation, forgoing surgery will eliminate the associated morbidity and mortality. Despite a large volume of studies reporting some promising results, no clinical, radiological, or biochemical features have demonstrated an ability to predict response with adequate sensitivity or specificity to guide treatment. Consequently, more robust data on sarcopenia, clinical and biochemical predictors of response is required to accurately assess which patients are likely to sustain a pCR.

Lastly, studies have highlighted potential drawbacks of adjuvant chemotherapy in rectal cancer including treatment delays and poor compliance. As a results of these challenges, several trials have advocated for systemic chemotherapy to be given preoperatively (TNT). Results of these advanced phase trials have shown that TNT can increase rates of cCR and pCR and improve DFS. Although therapy associated toxicities were more frequently observed in the TNT arm of these trials, this does not result in difference in compliance, surgical management and postoperative complications when compared to conventional nCRT. While TNT has increased in popularity, a major question relating to treatment sequencing remains unsolved. It is unclear whether consolidation chemotherapy is better than induction chemotherapy in all LARC patients or whether treatment sequencing should be tailored towards clinical stage at presentation.

CHAPTER 2: PRECIS

The work in this thesis is presented in three parts.

Part 1: Artificial intelligence assessment of nodal status on pre-operative imaging for colorectal cancer.

This part of the thesis describes the potential of using AI to predict the presence or absence of metastatic disease in local lymph nodes in CRC. In this section, we ask whether AI can improve on the current 70% accuracy of radiologists in nodal staging using the same imaging modality.

Chapter 3 presents a systematic review and meta-analysis aiming to determine the accuracy of deep learning algorithms and radiomics models compared with radiologist assessment in the diagnosis of lymphadenopathy in patients with abdominopelvic malignancies. **Chapter 4** is a systematic review and meta-analysis that updates the available evidence on the accuracy of deep learning algorithms and radiomics models compared with radiologist assessment in the diagnosis of lymphadenopathy solely focused on patients with CRC. To establish a baseline accuracy of preoperative lymph node staging in colon cancer based on local experience, in **Chapter 5**, a prospective cohort study was conducted at the Royal Adelaide Hospital and St Andrews Hospital to assess the diagnostic accuracy of multidisciplinary team and radiology reporting of pre-operative CRC local staging. **Chapter 6** describes the development and assessment of a deep learning model used to diagnose local lymph nodes on preoperative staging CT scans in a cohort of 1201 patients with colon cancer. Using pathological confirmation from surgery as the gold standard, allowed us to classify patients into LN positive or LN negative. This study was designed from the beginning to address the knowledge gap identified in the previous chapters. Given the negative findings in a large cohort of patients and the failure of the deep learning model to outperform the radiologist's assessment of lymph nodes on preoperative staging CT, we shifted the focus towards the potential application of AI in sarcopenia diagnosis on CT imaging. **Chapter 7** is a systematic review and

meta-analysis aimed to assess the performance of CT-based AI segmentation models used for body composition analysis and sarcopenia diagnosis.

Part 2: Prediction of local response to chemoradiation in locally advanced rectal cancer.

The second part of this thesis focuses on predictors of response following neoadjuvant therapy for patients with LARC. We evaluated sarcopenia, clinical and biochemical factors to determine if they could predict local response after neoadjuvant therapy.

In **Chapter 8,** a retrospective cohort study was conducted to investigate the association between sarcopenia and tumour response after nCRT in patients with LARC. **Chapter 9** presents a retrospective cohort study relating to clinical and biochemical predictors of tumour response after neoadjuvant therapy in rectal cancer.

Part 3: Outcomes of a personalised Total Neoadjuvant Therapy (pTNT) protocol for the treatment of advanced rectal cancer.

In the last part of this thesis, we investigate whether Total Neoadjuvant Therapy sequencing should be tailored to clinical stage at presentation rather than a uniform protocol for all patients with advanced rectal cancer.

Chapter 10 examines short-term outcomes of a personalised Total Neoadjuvant Therapy (pTNT) protocol with treatment sequencing based on clinical stage at presentation. The protocol consisted of two-schema based on clinical stage, patients with distant failure risk received induction chemotherapy before nCRT and patients with locoregional failure risk received nCRT followed by consolidation chemotherapy. Finally, **Chapter 11** includes a multicentred retrospective comparative analysis between pTNT versus extended chemotherapy in the wait period (xCRT) versus standard Chemoradiotherapy (sCRT) in patients with LARC.

PART 1: ARTIFICIAL INTELLIGENCE ASSSESSMENT OF NODAL STATUS ON PRE-OPERATIVE IMAGING FOR COLORECTAL CANCER.

CHAPTER 3: ARTIFICIAL INTELLIGENCE FOR THE DIAGNOSIS OF LYMPH NODE METASTASES IN PATIENTS WITH ABDOMINOPELVIC MALIGNANCY: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Statement of Authorship

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Contribution to the Paper	Conception and design of the work Data acquisition Analysis and interpretation of data Drafting the final manuscript		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	01/08/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Conception and design of the work Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		
Signature		Date	01/08/2022

3.1 Abstract

Introduction: Accurate clinical diagnosis of lymph node metastases is of paramount importance in the treatment of patients with abdominopelvic malignancy. This review assesses the diagnostic performance of deep learning algorithms and radiomics models for lymph node metastases in abdominopelvic malignancies.

Methodology: Embase (PubMed, MEDLINE), Science Direct and IEEE Xplore databases were searched to identify eligible studies published between January 2009 and March 2019. Studies that reported on the accuracy of deep learning algorithms or radiomics models for abdominopelvic malignancy by CT or MRI were selected. Study characteristics and diagnostic measures were extracted. Estimates were pooled using random-effects meta-analysis. Evaluation of risk of bias was performed using the QUADAS-2 tool.

Results: In total, 498 potentially eligible studies were identified, of which 21 were included and 17 offered enough information for a quantitative analysis. Studies were heterogeneous and substantial risk of bias was found in 18 studies. Almost all studies employed radiomics models (n=20). The single published deep-learning model out-performed radiomics models with a higher AUROC (0.912 vs 0.895), but both radiomics and deep-learning models outperformed the radiologist's interpretation in isolation (0.774). Pooled results for radiomics nomograms amongst tumour subtypes demonstrated the highest AUC 0.895 (95%CI, 0.810 - 0.980) for urological malignancy, and the lowest AUC 0.798 (95%CI, 0.744 - 0.852) for colorectal malignancy.

Conclusion: Radiomics models improve the diagnostic accuracy of lymph node staging for abdominopelvic malignancies in comparison with radiologist's assessment. Deep learning models may further improve on this, but data remain limited.

3.2 Introduction

The most recent U.S. mortality data estimates suggest that 264,420 deaths per year are attributed to abdominopelvic malignancy.[135] For the majority of these tumours, particularly with the adenocarcinoma subtypes, the most likely initial sites of metastases are to locally draining Lymph Nodes (LN). Therefore, the status of these nodes remains a key factor in determining patient staging, treatment strategy, and survival.[7,136,137] For this reason, all national guidelines commonly recommend treatment options based directly on preoperative staging in this setting.[138-141]

Despite advances in medical imaging technology, the accurate clinical prediction of LN status remains difficult. Non-invasive imaging modalities such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) have been widely used for the evaluation of LN status with mixed results. As diagnostic accuracy of LN metastases depends largely on the level of training and experience of the radiologist, and the quality of the scanner itself, sensitivity and specificity may vary among studies. CT has reported accuracy rates as low as 60-78%% for determining LN metastases[142], along with sensitivity rates of 47% and specificity rates of 71%.[11] Similarly, the quality of preoperative LN staging using MRI in terms of sensitivity and specificity are 77-86% and 67-71%, respectively.[143-145]

Artificial Intelligence (AI) may have a promising role in this area, potentially overcoming some human limitations in diagnostic accuracy.[69,146] Radiomics models and deep-learning algorithms have shown promising results integrating CT and MRI for detection of LN metastases for selected indications.[147-149] However, despite numerous breakthrough studies demonstrating expert level diagnosis by AI models, currently there are no studies systematically assessing and summarising data on AI for abdominopelvic LN detection from source CT or MRI.

The purpose of this study is to conduct a systematic review and meta-analysis of published data on diagnostic accuracy of deep-learning algorithms and radiomics models for primary LN staging in patients with abdominopelvic malignancies.

3.3 Methods

3.3.1 Search strategy

A systematic search in Embase (PubMed, MEDLINE), Science Direct and IEEE Xplore Digital library was performed using Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[150] All potentially relevant studies from January 1, 2009 to March 31 2019 were identified. The following MeSH terms were used: “Artificial intelligence”, “machine learning”, “deep learning”, “convolutional neural network”, “automatic detection”, “computer-aided”, “Radiomic”, “Radiomics”, “CT”, “MRI”, “images”, “diagnostic imaging”, “radiology”, “lymph node”, “lymph nodes”, “lymph node detection” (Table 1). Additional studies were identified from hand-searching reference lists of all relevant articles.

Table 1 Search Strategy

Literature sources	**Search in**	**Limits**	**Search terms**
Science Direct	Advanced search	Research articles, years (2009-2019)	(“Artificial intelligence” OR “deep learning” OR “convolutional neural network” OR “automatic detection” OR “Radiomic” OR “Radiomics”) AND (“CT” OR “MRI”) AND (“Lymph node” OR “lymph node detection”)
Embase, (PubMed, MEDLINE)	Advanced search	N/A	('artificial intelligence'/exp OR 'artificial intelligence' OR 'machine learning'/exp OR 'machine learning' OR 'deep learning'/exp OR 'deep learning' OR 'convolutional neural network'/exp OR 'convolutional neural network' OR 'automatic detection' OR 'computer-aided' OR ‘Radiomic’ OR ‘Radiomics’) AND ('ct'/exp OR 'ct' OR 'mri'/exp OR 'mri' OR 'images' OR 'diagnostic imaging'/exp OR 'diagnostic imaging' OR 'radiology'/exp OR 'radiology') AND ('lymph node*' OR 'lymph node detection') AND ([article]/lim OR [article in press]/lim) AND [english]/lim AND [2009-2019]/py
IEEE Xplore Digital Library	Journals & Magazines	Years (2009-2019)	(“Artificial intelligence” OR “machine learning” OR “deep learning” OR “convolutional neural network” OR “automatic detection” OR “computer-aided” OR “segmentation” OR “Radiomic” OR “Radiomics”) AND (“CT” OR “MRI” OR “images” OR “diagnostic imaging” OR “radiology”) AND (“Lymph node*” OR “lymph node detection”)

3.3.2 Selection criteria

All original studies assessing radiomics models or deep-learning algorithms to analyse CT or MRI images with the purpose of detecting LN metastases in patients with abdominopelvic organ malignancy were included. Abdominopelvic organs were defined as: liver, gallbladder, kidneys, spleen, pancreas, stomach, small bowel, colon, rectum, bladder, and internal reproductive organs. The search was limited to studies published in English language. Studies focused on segmentation and feature extraction methods only, case reports, editorials, letters, meta-analysis, comments, mini-reviews, book chapters and all conference which did not include complete data were excluded.

Titles and abstracts were then screened after removing duplicates, for eligibility by three independent reviewers (S.B., N.N.DV. and G.M.) using Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia (available at www.covidence.org). Discrepancies regarding inclusion and exclusion of specific studies were discussed and resolved by consensus.

3.3.3 Data extraction and quality assessment

The full texts of all eligible studies were then reviewed for reporting on the type of radiomics or deep-learning model, study characteristics and outcome measures. The following data was then extracted from each study: study type, total patient number, sample size for diagnostic accuracy, target area, image modality, reference gold standard, additional clinicopathological features and diagnostic endpoint. To obtain diagnostic accuracy data, we extracted True Positive (TP), False Positive (FP), True Negative (TN), False Negative (FN), and Area Under the receiver operating Curve (AUC) along with other parameters. The primary outcome of interest was AUC; other statistical measures of algorithmic performance such as sensitivity and specificity were evaluated separately. Two independent reviewers (S.B and N.N.DV) performed a quality assessment of selected studies by using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) criteria.[151]

3.3.4 Statistical Analysis

For the quantitative meta-analysis, the testing set results of studies that presented absolute numbers for AUC and their 95% confidence intervals, TP, FP, TN, FN or those that provided enough information to extract/derive the numbers manually. If results were not reported in an independent test set, cross validation results are reported. When different AI models were tested within the same paper, the proposed model in the paper with the highest diagnostic performance was used for analysis. Additionally, a sub-analysis was performed to estimate the accuracy of the radiologist's assessment derived from studies that reported this. The corresponding AUCs, sensitivities and specificities of radiologists were extracted in the same way as described above.

Two software packages MedCalc for Windows, version 16.4.3 (MedCalc Software, Ostend, Belgium) and RevMan, version 5.3.[152] were utilised for statistical analysis. Missing data were computed using formulas derived from a confusion matrix (Table 2) with the help of the above software packages. Forest plots were generated from pooling sensitivity, specificity and AUC data using random-effects model to incorporate the variability between studies.[153] To assess heterogeneity between studies the inconsistency index (I^2) was used. I^2 values below 50% indicated low heterogeneity, while values above 50% indicated substantial heterogeneity.[154] A funnel plot was also constructed to visually assess publication bias.

Table 2 Formulas

Number	Formula	Summary
1	$\frac{TP}{P} = \frac{TP}{TP + FN}$	Sensitivity
2	$\frac{TN}{N} = \frac{TN}{TN + FP}$	Specificity
3	$\frac{TP + TN}{P + N} = \frac{TP + TN}{TP + TN + FP + FN}$	Accuracy
4	$\frac{TP}{TP + FP}$	PPV
5	$\frac{TN}{TN + FN}$	NPV
6	$\frac{(Upper\ Limit - Lower\ Limit)}{3.92}$	SE

P, condition positive; N, condition negative; FN, false negative; FP, false positive; TN, true negative and TP, true positive; PPV, positive predictive value; NPV, negative predictive value; Upper limit, upper limit of confidence interval; Lower limit, lower limit of confidence interval; SE, standard error

3.4 Results

3.4.1 Study selection

The initial search identified 498 studies after duplicates were removed, and of these 414 studies were excluded based on screening of titles and abstracts, resulting in 58 studies for full-text review. A total of 21 articles met the inclusion criteria and were considered eligible for systematic review (Figure. 6).

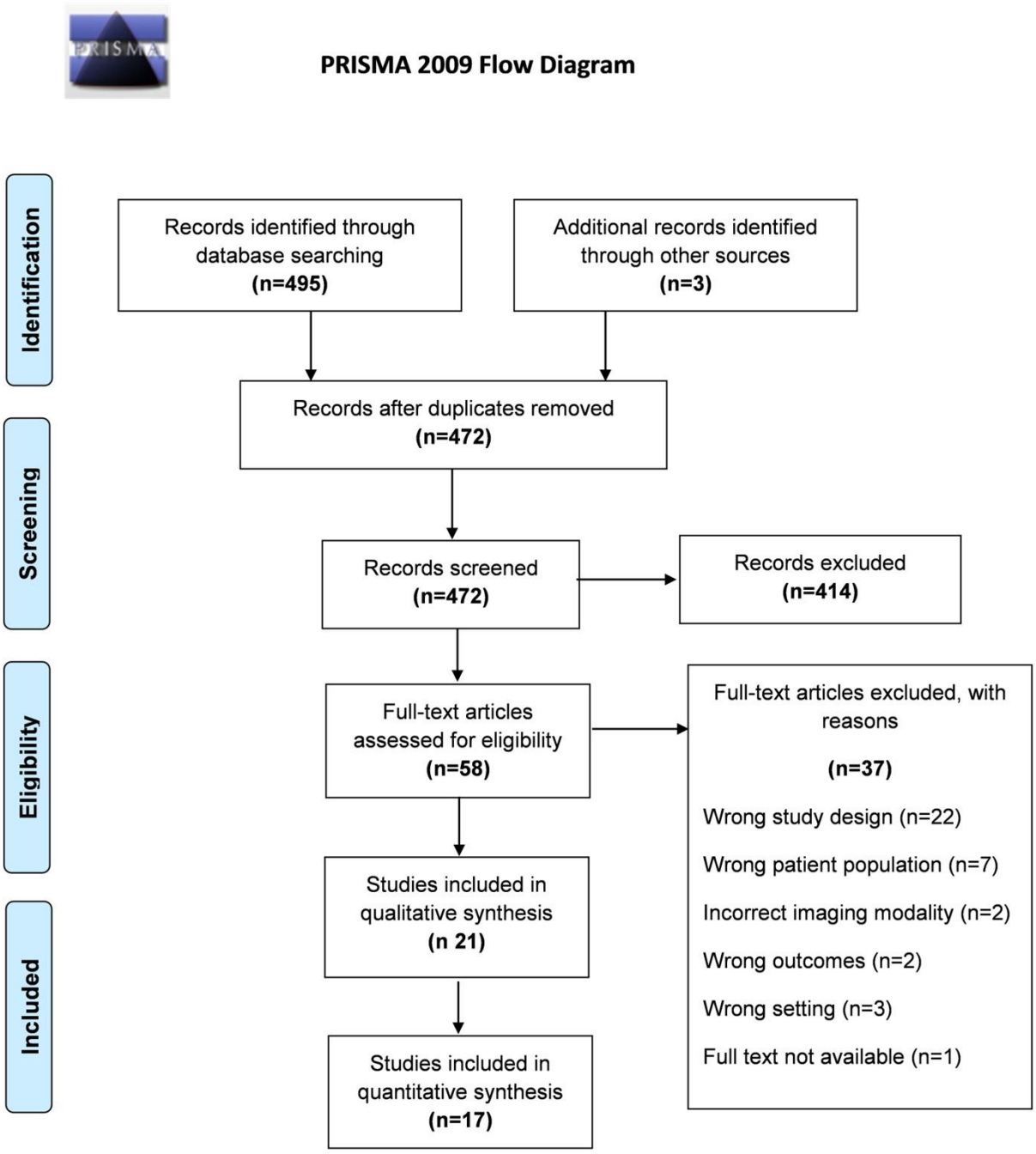

Figure. 6 Study Selection Process

3.4.2 Study characteristics

The characteristics of radiomics and deep-learning studies are summarized in Table 3. All included studies were published between 2011 and 2019. Of the 21 included studies, 17 had sufficient data for meta-analysis of AUC (Figure. 7), the patient cohorts were comprised of colorectal malignancies (4 studies), gynaecological malignancies (5 studies), hepatobiliary malignancies (2 studies), upper gastrointestinal malignancies (4 studies) and urological malignancies (2 studies). Reference standards were consistent across most malignancies and the modality of imaging being used. Most studies used pathology as the gold standard (20/21), only one study assigned a level of suspicion for each lymph node decided by a MD researcher and a radiologist to determine its reference standard.

Table 3 Characteristics of individual studies

First author	Year	Study type	Total Patients, n	Sample size for diagnostic accuracy, n	Target Area	Image modality	Reference Standard	Additional Clinicopathological features	Diagnostic endpoint
Colorectal									
Meng[155]	2019	Retrospective	345	148	Rectal cancer	MRI	Pathology	Age, sex, CEA level	Patient
Lu[147]	2018	Prospective	765	414	Rectal cancer	MRI	Pathology	-	Lymph Node
Chen[156]	2018	Prospective	115	33	Rectal cancer	ERUS,CT,SWE	Pathology	Age, gender, smoking history and laboratory tests	Patient
Huang[148]	2016	Retrospective	326	200	Colorectal cancer	CT	Pathology	CEA level, cN, histologic grade	Patient
Cai[157]	2012	Prospective	228	Avg of leave-one-out CV	Rectal cancer	CT	Pathology	-	Lymph Node
Tse[158]	2012	Retrospective	17	Avg of leave-one-out CV	Rectal Cancer	MRI	Pathology	-	Lymph Node (n=43)
Cui[159]	2011	Prospective	228	Avg of leave-one-out CV	Rectal cancer	CT	Pathology	-	Lymph Node (n=220)
Gynaecology									
Wang[149]	2019	Retrospective	96	29	Cervical cancer	MRI	Pathology	Age, histopathologic grade, cN	Patient
Kan[160]	2019	Retrospective	143	43	Uterine Cervical cancer	MRI	Pathology	-	Patient
Yu[161]	2019	Retrospective	153	51	Cervical cancer	MRI	Pathology	Clinical stage, tumour diameter, cLN, grey-level	Patient

								non-uniformity	
Wu[162]	2019	Retrospective	189	63	Cervical cancer	MRI	Pathology	$T2_{tumour+peri}$ + cN	Patient
Kim[163]	2011	Retrospective	143	Avg of leave-one-out CV	Uterine cervical cancer	MRI	Pathology	-	Lymph Node (n=680)
Hepatobiliary									
Ji[164]	2019	Retrospective	247	70	Biliary Tract cancer	CT	Pathology	cN	Patient
Ji[165]	2019 a	Retrospective	155	52	Biliary Tract cancer	CT	Pathology	CA 19-9 ≥ 1000 U/ml	Patient
Upper GI									
Jiang[166]	2019	Retrospective	1689	1017	Gastric cancer	CT	Pathology	cT stage and cN stage, differentiation status and CA199 level	Patient
Feng[167]	2019	Retrospective	490	164	Gastric cancer	CT	Pathology	-	Patient
Zhou[168]	2013	Retrospective	175	Avg of 5-fold CV	Gastric cancer	CT	Pathology	-	Patient
Zhang[169]	2011	Retrospective	175	Avg of 5-fold CV	Gastric cancer	CT	Pathology	-	Patient
Urology									
Wu[170]	2018	Retrospective	103	34	Bladder cancer	MRI	Pathology	cN	Patient
Wu[171]	2017	Retrospective	118	38	Bladder cancer	CT	Pathology	cN	Patient
Debats[172]	2011	Prospective	146	Avg of leave-one-out CV	Prostate cancer	MRI	CLOS	-	Lymph Node (n=2347)

CV, cross-validation; CT, computed tomography; MRI, magnetic resonance imaging; ERUS, endorectal ultrasound; SWE, shear-wave elastography; CEA, carcinoembryonic antigen; CLOS= classification based on level of suspicion

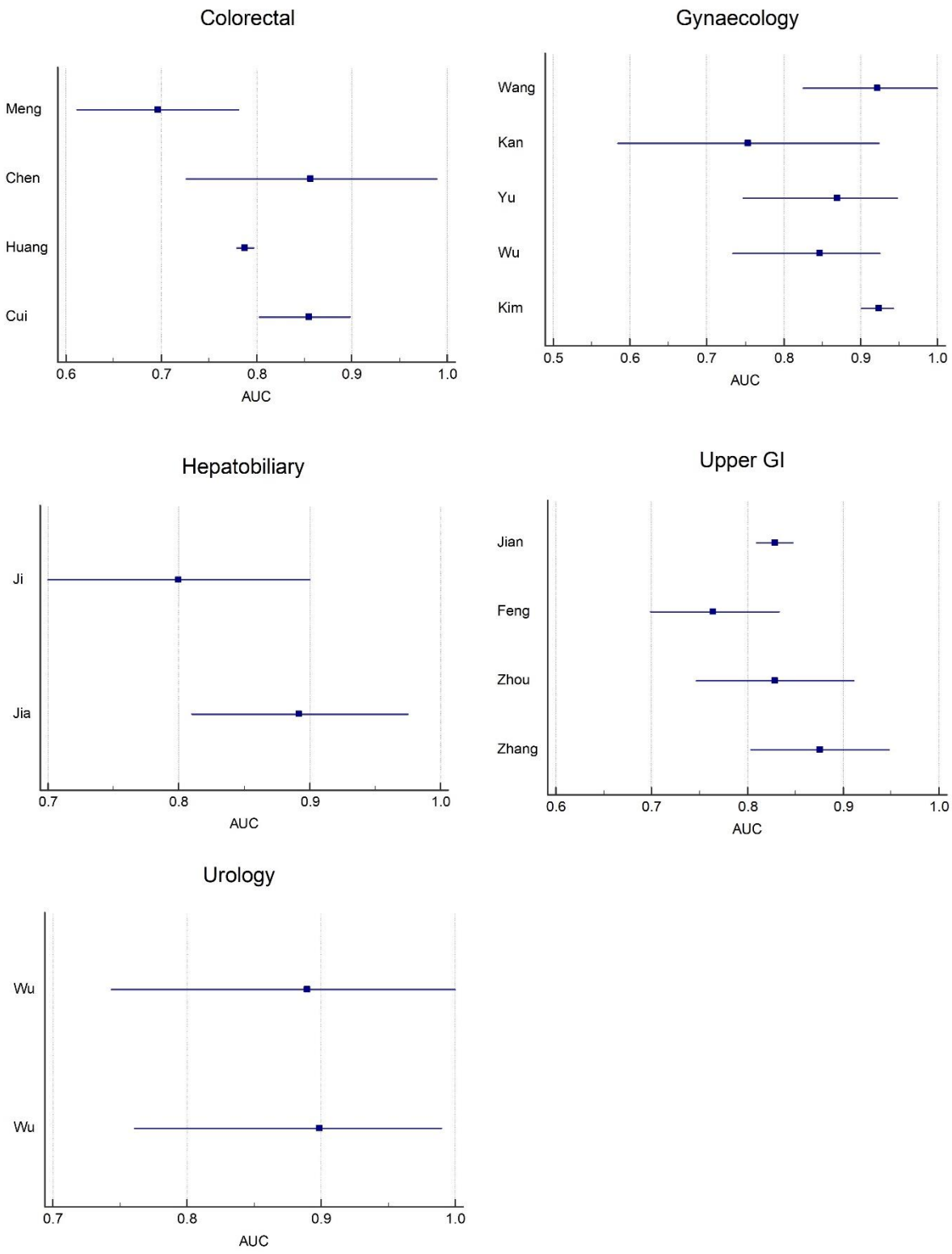

Figure. 7 Forest plots per surgical speciality

3.4.3 Quality Assessment

According to the QUADAS-2 tool, overall risk of bias in patient selection was high in 15 (71%) studies and low in six (29%) studies. Risk of bias in the index test was high in 12 studies (57%) and low in nine (43%). Risk of bias in the reference standard test was high in one study (4.8%) and low in 20 studies (95.2%). Flow and timing had all 21 studies with unclear risk of bias. Overall applicability concerns were low; however, three studies were judged to have high applicability concerns (Figure. 8). Individual evaluation of the risk of bias and applicability are shown in Table 4.

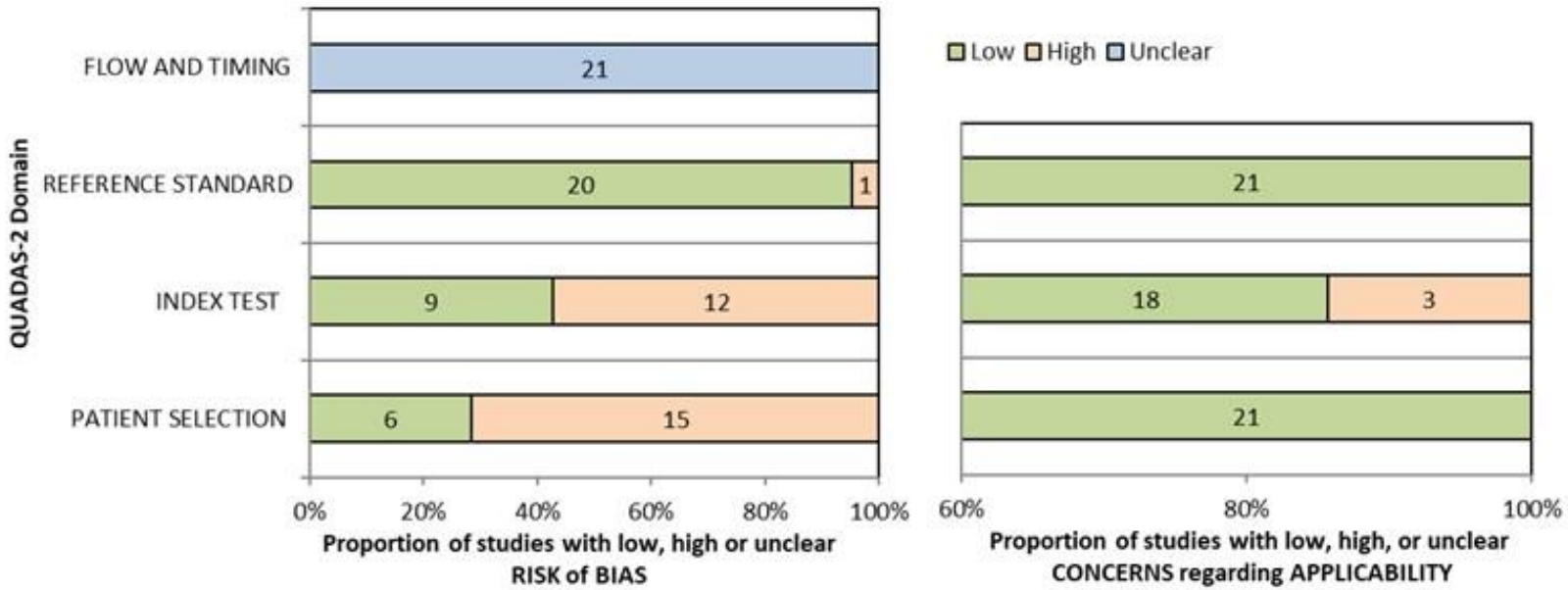

Figure. 8 The quality assessment of 21 included studies by QUADAS-2 tool

Table 4 Assessment of bias risk (BR) and applicability concerns (AP) of included studies using the QUADAS-2 tool

Study ID	Patient Selection (BR)	Index Test (BR)	Reference Standard (BR)	Flow and Timing (BR)	Patient Selection (AP)	Index Test (AP)	Reference Standard (AP)
Lu[147]	Low	Low	Low	Unclear	Low	Low	Low
Jiang[166]	High	High	Low	Unclear	Low	Low	Low
Ji[164]	High	Low	Low	Unclear	Low	Low	Low
Ji[165]	High	Low	Low	Unclear	Low	Low	Low
Wang[149]	High	High	Low	Unclear	Low	Low	Low
Feng[167]	High	Low	Low	Unclear	Low	Low	Low
Meng[155]	High	High	Low	Unclear	Low	High	Low
Kan[160]	Low	Low	Low	Unclear	Low	Low	Low
Yu[161]	High	High	Low	Unclear	Low	Low	Low
Wu[162]	High	High	Low	Unclear	Low	Low	Low
Chen[156]	Low	Low	Low	Unclear	Low	Low	Low
Wu[170]	High	Low	Low	Unclear	Low	Low	Low
Wu[171]	High	High	Low	Unclear	Low	Low	Low
Huang[148]	High	High	Low	Unclear	Low	Low	Low
Zhou[168]	High	Low	Low	Unclear	Low	Low	Low
Cai[157]	Low	High	Low	Unclear	Low	High	Low
Tse[158]	High	High	Low	Unclear	Low	Low	Low
Cui[159]	Low	High	Low	Unclear	Low	Low	Low
Debats[172]	Low	High	High	Unclear	Low	High	Low
Kim[163]	High	High	Low	Unclear	Low	Low	Low
Zhang[169]	High	Low	Low	Unclear	Low	Low	Low

3.4.4 Publication bias

To assess publication bias of the studies, a funnel plot of diagnostic AUC was constructed. The shape of the funnel plot revealed asymmetry within included studies (Figure. 9), supporting information). The funnel plot indicates between study heterogeneity and small study effects.

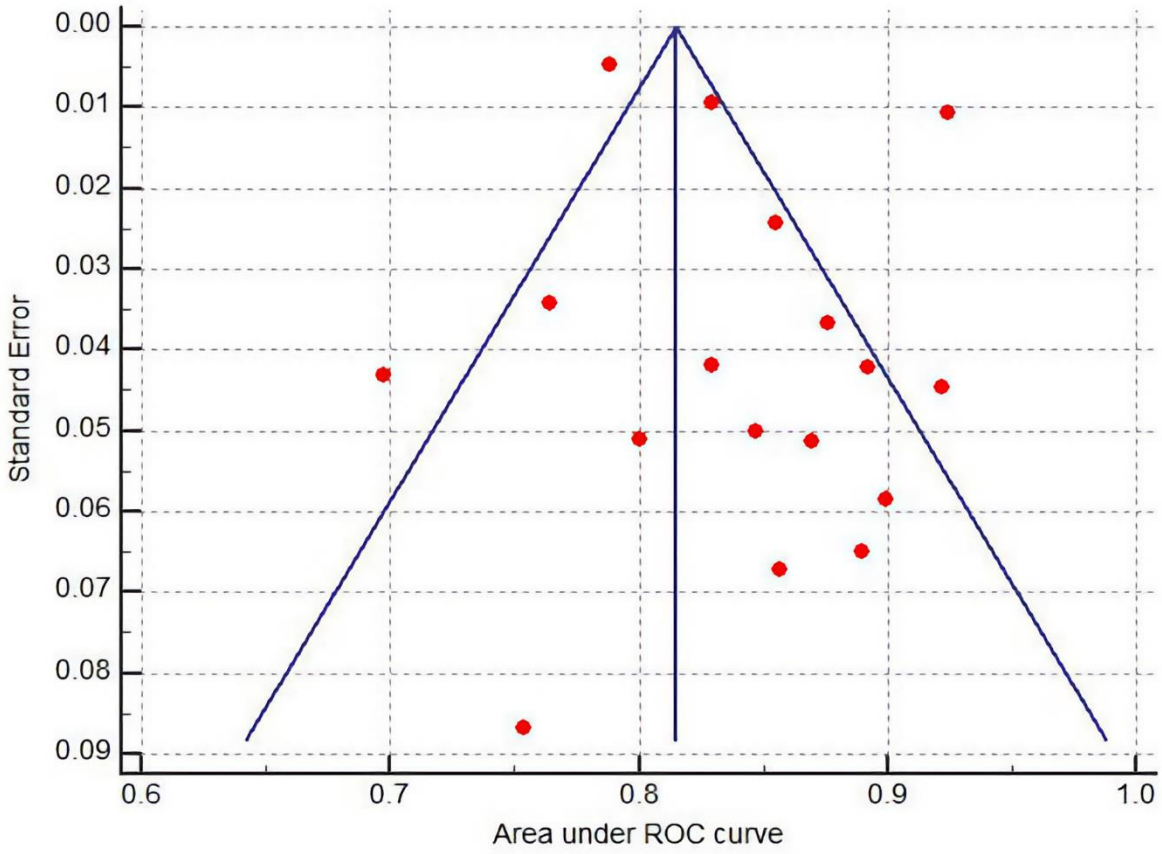

Figure. 9 Funnel plot of the area under the receiver operating characteristic (AUC) in 17 studies

3.4.5 Diagnostic Accuracy

Table 5 presents analysis of AUC achieved by the AI models and their performance in various surgical specialties. The one study using deep learning achieved the highest diagnostic accuracy with an AUC of 0.912 in urological malignancy. Based on the 17 studies that were included in the quantitative analysis, the highest AUC overall was seen in urological malignancy (AUC 0.895, 95%CI, 0.810 - 0.980), followed by gynaecological malignancy (AUC 0.893, 95%CI, 0.847 - 0.939). Hepatobiliary and upper gastrointestinal malignancies had similar AUCs of 0.851 (95%CI, 0.761 - 0.940) and 0.825 (95%CI, 0.789 - 0.860), respectively. It should be noted that the two hepatobiliary malignancy studies used their entire cohort from the training phase to test their radiomics model during the testing phase, likely overestimating the pooled AUC. Colorectal malignancies had the lowest AUC with a pooled value of 0.798 (95%CI, 0.744 - 0.852).

In terms of radiologist performance, the highest pooled AUC was again seen in urological malignancy (AUC 0.774, 95%CI, 0.672 - 0.875), followed by gynaecological (AUC 0.749, 95%CI, 0.656 - 0.842) and upper gastrointestinal (AUC 0.740, 95%CI, 0.712 - 0.767) malignancy. The lowest two AUCs were seen in colorectal malignancy (AUC 0.636, 95%CI, 0.586 - 0.686) and hepatobiliary malignancy (AUC 0.633, 95%CI, 0.549 - 0.716). Heterogeneity among radiologist assessment pooling was low with an I^2 value of 0%. Detailed assessment measures of deep learning, radiomics models and radiologists reported by individual studies are available in Table 6 and Table 7.

Table 5 Summary estimates for AUCs per surgical specialty					
Variable	**Studies (n)**	**Patients (n)**	**Summary Estimate (95%CI)**	**Heterogeneity (I^2, %)**	**Heterogeneity P Value**
Deep learning					
Colorectal	1	765	0.912	-	-
Radiomics					
Colorectal	4	607	0.798 (0.744 - 0.852)	77.0	0.005
Gynaecology	5	220	0.893 (0.847 - 0.939)	41.8	0.143
Hepatobiliary	2	402	0.851 (0.761 - 0.940)	48.3	0.164
Upper GI	4	1531	0.825 (0.789 - 0.860)	42.5	0.156
Urology	2	72	0.895 (0.810 - 0.980)	0	0.918
Radiologist					
Colorectal	2	181	0.636 (0.586 - 0.686)	0	0.650
Gynaecology	2	144	0.749 (0.656 - 0.842)	0	0.566
Hepatobiliary	2	402	0.633 (0.549 - 0.716)	0	0.945
Upper GI	1	1017	0.740 (0.712 - 0.767) [c]	-	-
Urology	2	72	0.774 (0.672 - 0.875)	0	0.4327

AUC, area under the receiver operating characteristic; CI, confidence interval; GI, gastrointestinal

Table 6 Results of individual studies

First author	P	N	TP	FP	TN	FN	PPV,%	NPV,%	Sensitivity,%	Specificity,%	Accuracy,%	AUC	95%CI	Standard Error [c]
Colorectal														
Meng[155]	63	83	46 [c]	36 [c]	47 [c]	17 [c]	56.1 [c]	73.4 [c]	73.0	56.6	63.7	0.697	0.612 - 0.781	0.0431
Lu[147]	-	-	-	-	-	-	-	-	-	-	-	0.912	-	-
Chen[156]	14	19	-	-	-	-	-	-	-	-	-	0.857	0.726 - 0.989	0.0671
Huang[148]	101	99	-	-	-	-	-	-	-	-	-	0.788	0.779 - 0.797	0.0046
Cai[157]	-	-	-	-	-	-	-	-	89	82	88	-	-	-
Tse[158]	39	4	-	-	-	-	-	-	-	-	91.0	-	-	-
Cui[159]	75	153	67 [c]	28 [c]	125 [c]	8 [c]	70.7 [c]	93.8 [c]	89	82	88	0.855 [c]	0.803 - 0.898 [c]	0.0242
Gynaecology														
Wang[149]	-	-	-	-	-	-	-	-	-	-	-	0.922	0.825 - 1	0.0446
Kan[160 b]	14	29	10 [c]	8 [c]	21 [c]	4 [c]	55.6 [c]	84.0 [c]	71.4	72.4	72.1	0.754	0.584 - 0.924	0.0867
Yu[161]	15 [c]	36 [c]	13 [c]	9 [c]	27 [c]	2 [c]	59.1	93.1	86.7	75.0	78.4	0.870	0.747 - 0.948	0.0513
Wu[162]	14	49	14 [c]	15 [c]	34 [c]	0 [c]	48.2 [c]	100.0 [c]	100.0	69.3	76.2	0.847 [c]	0.734 - 0.925 [c]	0.0487
Kim[163]	70 [c]	610 [c]	59	85	525	11	41 [c]	98 [c]	84	86	86	0.924	0.901-0.943	0.0107
Hepatobiliary														
Ji[164]	125 [a]	122 [a]	90 [a]	29 [a]	93 [a]	35 [a]	75.6 [a]	72.7 [a]	72.0 [a]	76.2 [a]	74.1 [c]	0.800	0.700 - 0.900	0.0510
Ji[165]	68 [a]	87 [a]	59 [a]	23 [a]	64 [a]	9 [a]	72.0 [a]	87.8 [a]	86.8 [a]	73.6 [a]	79.4 [c]	0.892	0.810 - 0.975	0.0421
Upper GI														

Jiang [166]	696	321	-	-	-	-	-	-	-	-	-	0.829	0.810 - 0.847	0.0094
Feng[167]	-	-	-	-	-	-	82.0	50.0	72.6	68.1	71.3	0.764	0.699 - 0.833	0.0342
Zhou[168]	134	41	120 [c]	8 [c]	33 [c]	14 [c]	93.6 [c]	70.0 [c]	89.5	80.0	87.4	0.829	0.747 - 0.911 [c]	0.0418
Zhang[169]	134	41	119 [c]	9 [c]	32 [c]	15 [c]	93 [c]	67.6 [c]	88.5	78.5	86.2 [c]	0.876	0.804 to 0.948 [c]	0.0366
Urology														
Wu[170]	12	22	-	-	-	-	-	-	-	-	-	0.890	0.744 - 1	0.0653
Wu[171]	7	31	-	-	-	-	-	-	-	-	-	0.899	0.761 - 0.990	0.0584
Debats[172]	-	-	-	-	-	-	-	-	-	-	-	0.935	-	-

[a] Values extracted from testing set comprised of full cohort.

[b] Values extracted from radiomic signature.

[c] Manually calculated values using eq. (1,2,3,4,5,6)

P, condition positive; N, condition negative; FN, false negative; FP, false positive; TN, true negative and TP, true positive; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver operating characteristic; CI, confidence interval

Table 7 Comparison between radiomics and radiologist in included studies									
First Author	**Radiomics models**				**Radiologist**				**P Value**
	Sensitivity, %	**Specificity, %**	**AUC**	**95%CI**	**Sensitivity, %**	**Specificity, %**	**AUC**	**95%CI**	
Colorectal									
Meng[155]	73.0	56.6	0.697	0.612 - 0.781	70.4	55.9	0.632 [c]	0.578 - 0.683 [c]	-
Chen[156]	-	-	0.857	0.726 - 0.989	-	-	0.671	0.511 - 0.831	0.012
Gynaecology									
Yu[161]	86.7	75.0	0.870	0.747 - 0.948	-	-	0.772	0.633 - 0.878	-
Wu[162]	100.0	69.3	0.847	0.749 - 0.945 [c]	43.1	100.0	0.717	0.574 - 0.859 [c]	-
Hepatobiliary									
Ji[164]	72.0 [a]	76.2 [a]	0.800	0.700 - 0.900	43.2 [a]	83.6 [a]	0.630	0.520 - 0.740	-
Ji[165]	86.8 [a]	73.6 [a]	0.892	0.810 - 0.975	-	-	0.636	0.507 - 0.764	-
Upper GI									
Jiang [166]	-	-	0.829	0.810 - 0.847	77.9 [c]	70.1 [c]	0.740[c]	0.712 - 0.767 [c]	-
Urology									
Wu[170]	-	-	0.890	0.744 - 1	-	-	0.727	0.573 - 0.882	-
Wu[171]	-	-	0.899	0.761 - 0.990	71.4 [c]	90.3 [c]	0.809 [c]	0.649 - 0.918 [c]	-

AUC, area under the receiver operating characteristic; CI, confidence interval

3.5 Discussion

Due to the widespread application of AI in medical imaging in recent times, radiomics and deep-learning models are now being actively evaluated for LN staging in a variety of malignancy types. To our knowledge, this is the first systematic review of AI system performance in the diagnosis of metastatic regional LN in abdominopelvic malignancy. Our review demonstrates variability in the accuracy depending on tumour type, but a promising improvement upon radiologist's interpretation, which is the current standard of care. In addition, it is possible that deep learning methods will further improve upon existing radiomics models.

Radiomics is a set of hand-design features/characteristics that are automatically computed from the image. These features are then used by a classifier/algorithm to produce a diagnosis. Radiomics models, better known as nomograms, incorporate the radiomics signature with clinical variables to enable superior prediction by improving pre-test probability.[148] On the contrary, deep-learning models, such as Convolutional Neural Networks (CNNs) are a relatively new type of algorithm that can produce the diagnosis by automatically learning the optimal features for producing such diagnosis, without human defined parameters.[173] Deep learning models have been shown to perform relatively well in many tasks and to outperform radiomics models. However they require large data sets to achieve a competitive performance.[174,175]

Most included studies investigating the use of AI in LN detection for abdominopelvic malignancies employed radiomics (n=20), with only one study using deep learning. There were few prospective studies (n=5), with the majority being retrospective with clinical data collected from case notes, and radiology and pathology reports. Several radiomics studies have critical limitations typical of diagnostic studies, such as limited sample size, lack of external validation and potential overfitting. Moreover, radiomics models developed using imaging obtained from a single scanner may produce a lack of generalizability and selection bias. Image acquisition from multiple scanner types is

preferable when developing an AI model for the general population. Significantly, several studies failed to address the disproportionate sample size between node positive and node negative patients and did not discuss how this imbalance may have affected the analysis. The reproducibility and clinical value of the AI model should be tested using an independent cohort. However, two of the radiomics studies used their entire cohort from the training phase during the testing phase of their model, rather than using a new cohort of patients.[164,165] This probably meant that both studies would have over-optimistic AUCs, as their proposed models would re-identify the same imaging features seen in the training phase as in the testing phase. There was high heterogeneity among studies in both the radiomics models and radiology subgroups. The high heterogeneity observed among subgroups may have been attributed to differences in population and the small sample sizes in each included study.

The use of an appropriate label for the presence or absence of lymphadenopathy in the development of radiomics and deep learning models is another issue to be considered. Both models typically incorporated the radiologist's diagnosis into the algorithm and failed to designate the pathological or surgical diagnosis as the ground truth when labelling their training cohort. Therefore, model accuracy tended to bias towards the radiologist's assessment, which is a problem since for many abdominopelvic malignancies radiologist assessment accuracy has historically been quite limited.[11,142] In the future, we suggest labelling the training cohort with pathological staging, this alternative may help newly developed deep learning algorithms to outperform existing algorithms training with radiological staging.

The current review found 11 studies that reported on diagnostic performance of the radiologist. Most studies approached the assessment of radiomics or deep learning models in isolation, but two studies specifically compared radiomics with the radiologist's assessment and found a significant difference favouring the radiomics model.[176,177] A recent meta-analysis performed by Liu and Faes et al. found

diagnostic performance of deep-learning models to be equivalent to that of health-care professionals for rectal cancer staging.[155] However, evidence comparing deep-learning versus radiologists for LN metastases detection in abdominopelvic malignancies remains scarce, which limits our ability to extrapolate the diagnostic benefit of these systems in healthcare delivery.

This meta-analysis has several limitations. Firstly, the analysis was not separated between per-patient and per-nodal basis, which could potentially have skewed the data in favour of a higher pooled AUC (by artificially increasing the n). Secondly, there were a substantial number of studies in which some of the required test performance measures were not published and subsequently the value was calculated manually. The variability between different patient populations, scanner technology, and criteria for LN metastases may also have affected the accuracy of the results. Lastly, due to the high heterogeneity of studies, the pooled estimated of the quantitative results must be interpreted with caution.

3.6 Conclusion

Radiomics models improve the diagnostic accuracy of lymph node staging for abdominopelvic malignancies in comparison with radiologist's assessment. Deep learning models may further improve on this, but data remain limited.

CHAPTER 4: ARTIFICIAL INTELLIGENCE FOR PRE-OPERATIVE LYMPH NODE STAGING IN COLORECTAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Statement of Authorship

Title of Paper	Artificial intelligence for pre-operative lymph node staging in colorectal cancer: a systematic review and meta-analysis
Publication Status	Published
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Name of Principal Author (Candidate)	Sergei Bedrikovetski		
Contribution to the Paper	Conception and design of the work Data acquisition Analysis and interpretation of data Drafting the final manuscript		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	01/07/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Signature		Date	01/07/2022

4.1 Abstract

Introduction: Artificial Intelligence (AI) is increasingly being used in medical imaging analysis. We aimed to evaluate the diagnostic accuracy of AI models used for detection of lymph node metastasis on pre-operative staging imaging for colorectal cancer.

Methods: A systematic review was conducted according to PRISMA guidelines using a literature search of PubMed (MEDLINE), EMBASE, IEEE Xplore and the Cochrane Library for studies published from January 2010 to October 2020. Studies reporting on the accuracy of radiomics models and/or deep learning for the detection of lymph node metastasis in colorectal cancer by CT/MRI were included. Conference abstracts and studies reporting accuracy of image segmentation rather than nodal classification were excluded. The quality of the studies was assessed using a modified questionnaire of the QUADAS-2 criteria. Characteristics and diagnostic measures from each study were extracted. Pooling of area under the receiver operating characteristic curve (AUROC) was calculated in a meta-analysis.

Results: Seventeen eligible studies were identified for inclusion in the systematic review, of which 12 used radiomics models and five used deep learning models. High risk of bias was found in two studies and there was significant heterogeneity among radiomics papers (73.0%). In rectal cancer, there was a per-patient AUROC of 0.808 (0.739-0.876) and 0.917 (0.882-0.952) for radiomics and deep learning models, respectively. Both models performed better than the radiologists who had an AUROC of 0.688 (0.603 to 0.772). Similarly in colorectal cancer, radiomics models with a per-patient AUROC of 0.727 (0.633-0.821) outperformed the radiologist who had an AUROC of 0.676 (0.627-0.725).

Conclusion: AI models have the potential to predict lymph node metastasis more accurately in rectal and colorectal cancer, however, radiomics studies are heterogeneous and deep learning studies are scarce.

4.2 Introduction

Colorectal Cancer (CRC) is the second most common malignancy and the third leading cause of cancer-related mortality in the world, accounting for 862,000 deaths annually.[178] CRC nodal metastases play a pivotal role in disease-free survival and in determining appropriate adjuvant and neoadjuvant treatment.[179] As a result of the application of preoperative staging MRI in patients with rectal cancer, neoadjuvant chemoradiation has become the standard of care in locally advanced tumours, resulting in improved local control and resectability. Owing to the lower accuracy of lymph node staging in colon cancer at diagnosis, neoadjuvant treatment is not as commonly recommended.[15,139] However, this may change following the results of the recent Fluoropyrimidine, Oxaliplatin and Targeted Receptor Pre-Operative Therapy (FOXTROT) trial showing the safety and efficacy of neoadjuvant chemotherapy in patients with locally advanced colon cancer.[180] Therefore, improved accuracy in clinical nodal staging at diagnosis may become critical in surgical planning and targeting effective neoadjuvant treatment for these patients.[181,182]

Clinical staging of CRC is typically performed by radiologists assessing contrast enhanced Computer Tomography (CT) images in patients with colorectal cancer, and in addition, Magnetic Resonance Imaging (MRI) in patients with rectal cancer. The staging accuracy of CT and MRI is affected by multiple factors, such as equipment performance, standardised imaging protocols, the reporting radiologist's experience, and patient-specific factors. Overall, published series have reported a 70% accuracy of diagnosing lymph node metastasis on CT, and 69% on MRI using standard criteria.[11,183]

Current staging paradigms with its limited diagnostic and staging accuracy may be able to overcome by using Artificial Intelligence (AI) models. AI-enabled radiomics involves the extraction of a large number of investigator defined features from medical images using advanced computational algorithms.[184] While radiomics models have been used to predict lymph node

metastasis in CRC with partial success, previous studies by Ding et al. and Wang et al. demonstrate that deep learning algorithms have the potential to identify more subtle patterns that may elude conventional radiological and statistical methods.[185-187] Deep learning is a technique that involves the use of convolutional neural networks to self-educate an algorithm based on useful representations of images, thus bypassing the step of extracting manually designed features.[66] In recent years, radiomics nomograms and deep learning models have started to make a meaningful contribution to radiological diagnoses.[188]

The aim of this systematic review and meta-analysis is to evaluate the accuracy of AI models in diagnosing lymph node metastasis on CT and/or MRI in colorectal cancer patients.

4.3 Methods

4.3.1 Search Strategy

This systematic review and meta-analysis was performed according to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines and was registered with the International Prospective Register of Systematic Reviews with an analysis plan prior to conducting the research. A systematic search of the Cochrane Library, PubMed (MEDLINE), EMBASE and IEEE Xplore databases was performed for studies published between January 1st 2010 and October 1st 2020. The following search terms were used: artificial intelligence, deep learning, convolutional neural network, machine learning, automatic detection, radiomics, radiomic, CT/MRI, lymph node, lymph node metastasis, colon, rectal, colorectal (Appendix B: Table 1). Reference lists of articles retrieved were also searched manually to identify additional eligible studies.

4.3.2 Study Selection

Articles were included if they met the following criteria: (1) included patients with histopathological diagnosis of CRC; (2) developed or used a radiomics or deep learning algorithm to assess CT or MRI pre-operative lymph node metastasis detection and (3) published in English language. Exclusion criteria were (1) case reports, review articles, editorials, letters, comments, and conference abstracts; (2) studies focusing on segmentation or feature extraction methods only and (3) animal studies. After removing duplicates, titles and abstracts were reviewed for eligibility by two independent reviewers (SB and NNDV) using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia, available at www.covidence.org). Any disagreements were resolved by consensus arbitrated by a third author (TS).

4.3.3 Data Extraction

Data from selected full-text articles were reviewed for reporting on the type of radiomics or deep learning model, study characteristics and outcome measures. The extracted data included the first author, year of publication, country, study type, number of patients, sample size for diagnostic accuracy, age, imaging modality, type of malignancy, AI model, and referenced standard. Data related to the accuracy of the radiologists' assessment derived from studies using clinical nodal staging or clinical nomograms solely based on N-staging was also collected. To obtain diagnostic accuracy data of AI models and radiologists' assessment, two-by-two contingency tables, sensitivity, specificity, accuracy, and Area Under the Receiver Operating Characteristic Curve (AUROC) were extracted or reconstructed. The primary endpoint was AUROC, secondary endpoints included sensitivity, specificity, and accuracy.

4.3.4 Quality Assessment and Publication Bias

The modified version as proposed by Sollini et al. of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to access the methodological quality of the included studies.[189] Minimum criteria for fulfilling each QUADAS-2 item were discussed by two reviewers

(SB and NNDV) and disagreements were resolved by consensus. Publication bias was assessed using the Egger regression test and is presented as a funnel plot of diagnostic AUROC.

4.3.5 Statistical Analysis

Meta-analysis was performed using testing set results of studies that presented absolute numbers for AUROC and 95% confidence intervals, contingency tables or provided sufficient information to derive the numbers manually. If results were not reported in an independent test set, cross validation or full test sample results are presented in this review. When results of different AI algorithms were reported in one article, the proposed algorithm with the highest diagnostic performance was analysed.

Three software packages, MedCalc for Windows, version 16.4.3 (MedCalc Software, Ostend, Belgium), RevMan, version 5.3.21 and Meta-DiSc version 1.4, were utilised for statistical analysis. Missing data were computed using confusion matrix calculator or manually derived using formulas in Appendix B: Table 2. Pooling sensitivity, specificity and AUROC data was conducted using the Mantel-Haenszel method (fixed-effects model) and the DerSimonian Laird method (random-effects model).[190,191] To assess heterogeneity between studies, the inconsistency index (I^2) was used.[192] Heterogeneity was quantified as low, moderate, and high, with upper limits of 25%, 50% and 75% for I^2, respectively. Forrest plots were drawn to show AUROC estimates in each study in relation to the summary pooled estimate. A funnel plot was constructed to visually assess publication bias.

4.4 Results

4.4.1 Study Selection

A total of 68 studies were identified and 53 remained after removing duplicates. Review of titles and abstracts left 25 studies for full-text review. Finally, 17 studies were included in the systematic

review, 12 of which could be used in the meta-analysis and five studies were excluded due to insufficient information (Figure 10).[47,157,185,186,193-205]

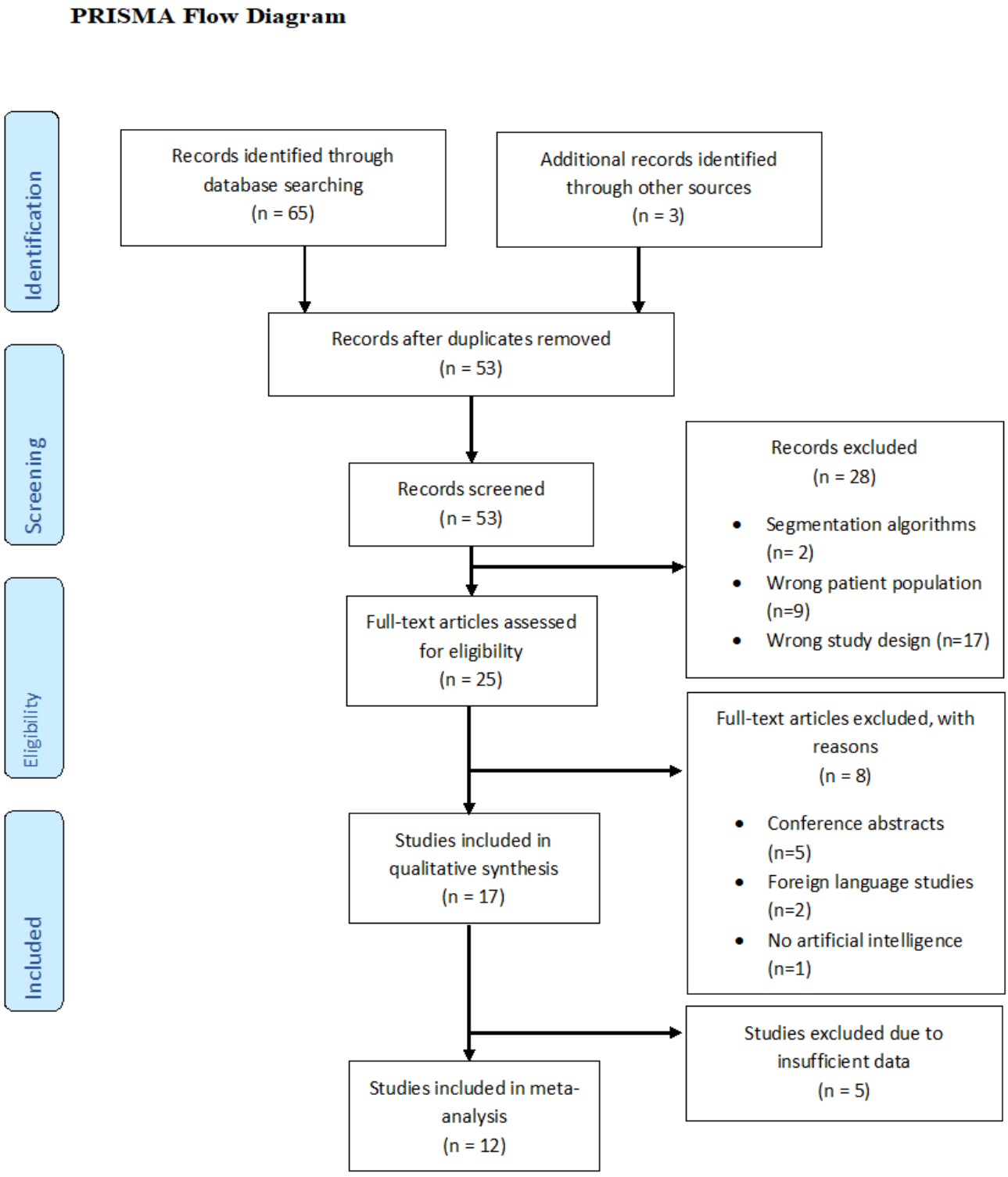

Figure. 10 PRISMA flow chart outlining the selection of studies for review.

4.4.2 Study Characteristics

Twelve studies used radiomics models and five used deep learning models (Appendix B: Table 3). All included studies were published between 2011 and 2020. Study design was retrospective in 11 and prospective in six studies. Fourteen studies were single-center and three were multi-center. Patients were predominantly male with a median age of 60 years (54 - 64). Eight studies used MRI and nine used CT to train their algorithm. The type of malignancy was colorectal in three studies, colon only in two, and rectal only in 12. Eleven studies used per-patient diagnostic output (the patient is node positive or negative) and 6 studies used per-nodal diagnostic output of lymph node metastasis (each individual node analysed separately). Fifteen studies used the postoperative pathology report as reference standard, and one study used a radiology report as the reference standard. The reference standard for the one remaining study was not reported.

4.4.3 Quality Assessment and Publication Bias

The methodologic quality of included studies is summarized in Figure 11. As per the QUADAS-2 tool, risk of bias in patient selection was low in 15 (88%) studies and high in two (12%) studies. Risk of bias in the index test was high in one study (6%) and low in 16 (94%). Risk of bias in the reference standard test was low in 15 (88%), high in one study (6%) and unclear in one study (6%). Flow and timing had all 17 studies with unclear risk of bias. Overall applicability concerns were low (Additional file 1: Table S4). Funnel plot assessment (Appendix B: Figure 1) showed no significant publication bias (Egger's intercept 1.11, 95%CI -1.22 to 3.42, p=0.313).

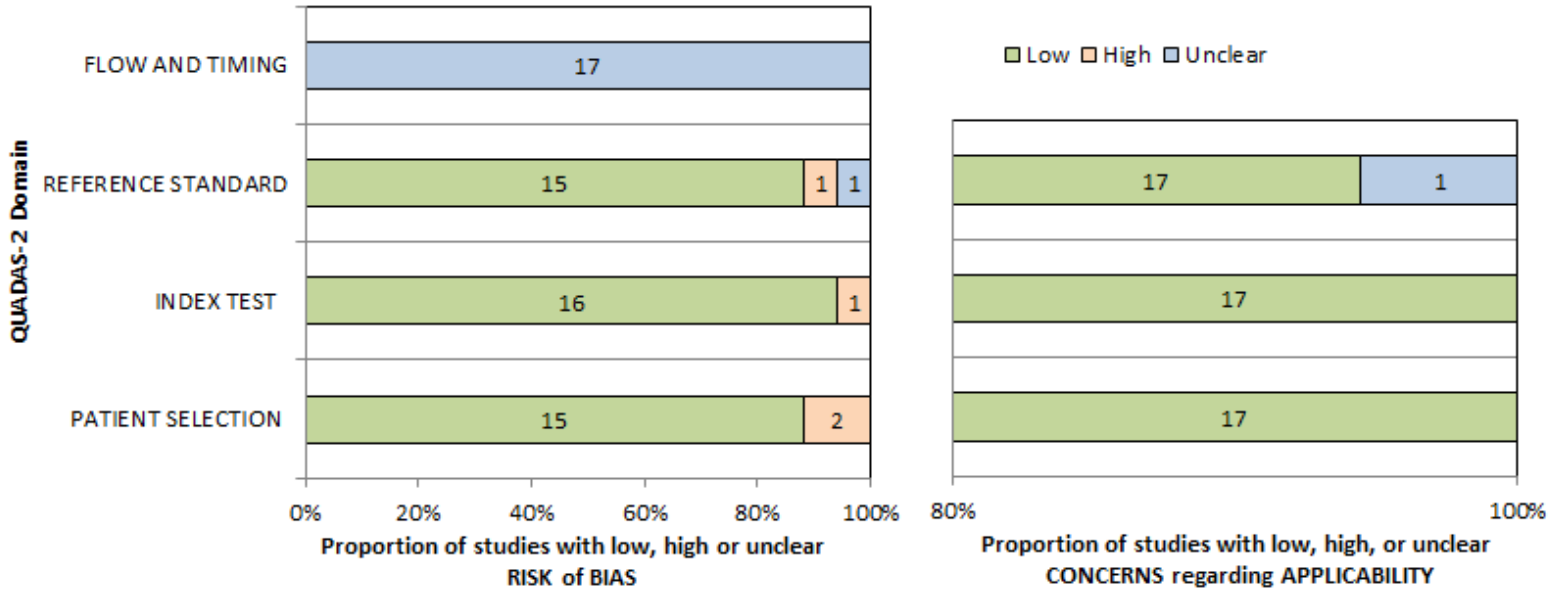

Figure. 11 Summary of QUADAS-2 assessments of included studies.

4.4.4 Diagnostic Accuracy

For the 12 studies that could be included in the quantitative analysis, 10 used radiomics and two used deep learning. For each outcome, summary estimates of sensitivity, specificity and AUROC were produced with 95% confidence intervals on a per-patient and per-nodal basis (Table 8). Pooled colorectal and rectal, per-patient and per-node detailed diagnostic measures reported by individual studies are shown in Table 9. The data for radiomics models in rectal cancer showed high heterogeneity with the exception of per-node AUROC and sensitivity. On a per-patient basis, radiomics in rectal cancer pooled AUROC was 0.808 (95%CI 0.739-0.876; Figure. 12) and pooled sensitivity and specificity were 0.776 (95%CI 0.685-0.851) and 0.676 (95%CI 0.608-0.739), respectively. On a per-nodal basis radiomics in rectal cancer pooled AUROC was 0.846 (95%CI 0.803-0.890) and pooled sensitivity and specificity were 0.896 (95%CI 0.834-0.941) and 0.743 (95%CI 0.665-0.811), respectively. On a per-patient basis radiomics in CRC pooled AUROC was 0.727 (95%CI 0.633-0.821). The radiologist per-patient assessment in rectal cancer pooled AUROC was 0.688 (95%CI 0.603 to 0.772), sensitivity was 0.678 (95%CI 0.628-0.726) and specificity was 0.701 (95%CI 0.667-0.733). Further, the radiologists per-patient assessment in CRC pooled AUROC was 0.676 (95%CI 0.627-0.725), sensitivity was 0.641 (95%CI 0.577-0.702) and specificity was 0.657 (95%CI 0.597-0.713). The deep learning data demonstrated low heterogeneity (I^2=0.00%, p=0.829), and on a per-patient basis, deep learning models outperformed radiomics and radiologist assessment in rectal cancer with an AUROC of 0.917 (95%CI 0.882-0.952). Deep learning sensitivity and specificity were reported in a single study as 0.889 and 0.935, respectively (Table 9).

Table 8 Pooled results of per-patient and per-node diagnosis from deep learning, radiomics and radiologists

Variable	Studies analysed	Type of malignancy	No. of studies	Pooled results (95% CI)	Heterogeneity (I^2, %)	Heterogeneity P Value
Deep learning						
AUROC per-patient	[185,186]	Rectal	2	0.917 (0.882-0.952)	0.00	0.829
Radiomics						
Sensitivity per-patient	[195,197,198]	Rectal	3	0.776 (0.685-0.851)	0.00	0.368
Sensitivity per-node	[199,204]	Rectal	2	0.896 (0.834-0.941)	0.00	0.393
Specificity per-patient	[195,197,198]	Rectal	3	0.676 (0.608-0.739)	75.4	0.017
Specificity per-node	[199,204]	Rectal	2	0.743 (0.665-0.811)	87.8	0.004
AUROC per patient	[194,203]	Colorectal	2	0.727 (0.633-0.821)	94.1	<0.0001
AUROC per patient	[195-198,202]	Rectal	5	0.808 (0.739-0.876)	63.3	0.028
AUROC per node	[199,204]	Rectal	2	0.846 (0.803-0.890)	0.00	0.433
Radiologist						
Sensitivity per-patient	[194,203]	Colorectal	2	0.641 (0.577-0.702)	70.9	0.064
Specificity per-patient	[194,203]	Colorectal	2	0.657 (0.597-0.713)	11.1	0.289
Sensitivity per-patient	[195-198]	Rectal	4	0.678 (0.628-0.726)	57.5	0.070
Specificity per-patient	[195-198]	Rectal	4	0.701 (0.667-0.733)	97.8	<0.0001
AUROC per-patient	[194,203]	Colorectal	2	0.676 (0.627-0.725)	58.4	0.121

AUROC per-patient	195-198,202	Rectal	5	0.688 (0.603 to 0.772)	93.4	<0.0001

AUROC, area under the receiver operating characteristic; CI, confidence interval

Table 9 Results for deep learning radiomics models and radiologist in accuracy to detect lymph node metastasis

First author	TP	FP	TN	FN	PPV, %	NPV, %	Sensitivity ,%	Specificity ,%	Accuracy, %	AUROC	95%CI	Standard Error [c]
Deep learning												
Per-patient												
Ding [186]	-	-	-	-	-	-	-	-	-	0.920	0.876-0.964	0.0224
Wang[185]	40	4	58	5	90.9	92.1	88.9	93.5	91.6	0.912 [c]	0.842-0.958	0.0296
Glaser[47 a]	-	-	-	-	-	-	-	-	-	0.860	-	-
Per-node												
Lu[200]	-	-	-	-	-	-	-	-	-	0.912	-	-
Li[201]	-	-	-	-	-	-	-	-	94.4	-	-	-
Radiomics												
Per-patient												
Eresen[193]	29 [c]	6 [c]	33 [c]	10 [c]	82.8 [c]	76.7 [c]	74.36	84.62	79.49	0.825	0.778-0.872	0.0240
Li[194]	69 [c]	44 [c]	128 [c]	67 [c]	61.06	65.64	50.74	74.42	63.96	0.650	0.583–0.713	0.0331
Yang[195]	13 [c]	5 [c]	21 [c]	2 [c]	73.2 [c]	90.5 [c]	85.0	82.0	83.0	0.780	0.630-0.920	0.0740
Nakanishi[196]	-	-	-	-	-	-	-	-	-	0.900	0.800-0.990	0.0485
Zhou[197]	24 [c]	27 [c]	74 [c]	5 [c]	47.1	93.7	82.8	73.3	75.4	0.818	0.731-0.905	0.0444
Meng [198]	46 [c]	36 [c]	47 [c]	17 [c]	56.1 [c]	73.4 [c]	73.0	56.6	63.7	0.697	0.612-0.781	0.0431
Chen[202]	-	-	-	-	-	-	-	-	-	0.857	0.726-0.989	0.0671
Huang[203]	-	-	-	-	-	-	-	-	-	0.788	0.779-0.797	0.0046
Per-node												
Zhu[199]	18 [c]	21 [c]	32 [c]	1 [c]	46.2	97.0	94.7	60.4	69.4 [c]	0.812	0.703−0.895	0.0490
Cai[157]	-	-	-	-	-	-	89	82	88	-	-	-
Tse[205]	-	-	-	-	-	-	-	-	91.0	-	-	-
Cui[204]	111 [c]	17 [c]	78 [c]	14 [c]	86.7 [c]	85.0 [c]	89	82	88	0.855 [c]	0.801-0.898 [c]	0.0247
Radiologist												

Per-patient												
Li[194] [d]	94 [c]	63 [c]	109 [c]	42 [c]	59.9	72.2	69.1	63.4	65.9	0.708	0.645–0.765	0.0306
Eresen[193]	33 [c]	23 [c]	16 [c]	6 [c]	58.9 [c]	72.7 [c]	84.6	41.0	62.8	0.772	0.718-0.825	0.0273
Yang[195]	41	41	43	14	50.0	75.4	74.6	51.2	60.4	0.629 [c]	0.543-0.709 [c]	0.0423
Nakanishi[196] [b]	71	0	147	29	100.0	83.5	71.0	100.0	88.3 [c]	0.855 [c]	0.805-0.896 [c]	0.0232
Zhou[197] [b]	49	89	215	38	35.5	85.0	56.3	70.7	67.5	0.635	0.585-0.683	0.0250
Meng[198] [b]	88 [c]	96 [c]	124 [c]	37 [c]	47.8 [c]	77.0 [c]	55.9	70.4	61.3	0.632 [c]	0.578-0.683 [c]	0.0268
Chen[202]	-	-	-	-	-	-	-	-	-	0.671	0.511-0.831	0.0816
Huang[203]	58 [c]	30 [c]	69 [c]	43 [c]	65.9 [c]	61.6 [c]	57.4 [c]	69.7 [c]	63.5 [c]	0.636 [c]	0.565-0.702 [c]	0.0349
Per-node												
Cui[204]	39 [c]	101 [c]	52 [c]	36 [c]	27.7 [c]	59.1 [c]	52 [c]	34 [c]	39.9 [c]	0.430 [c]	0.365-0.497 [c]	0.0337

[a] Values extracted from training set.

[b] Values extracted from total cohort.

[c] Manually derived/reconstructed values using formulas from Additional file 1: Table S2

[d] Values extracted from clinical models

FN, false negative; FP, false positive; TN, true negative and TP, true positive; PPV, positive predictive value; NPV, negative predictive value; AUROC, area under the receiver operating characteristic; CI, confidence interval

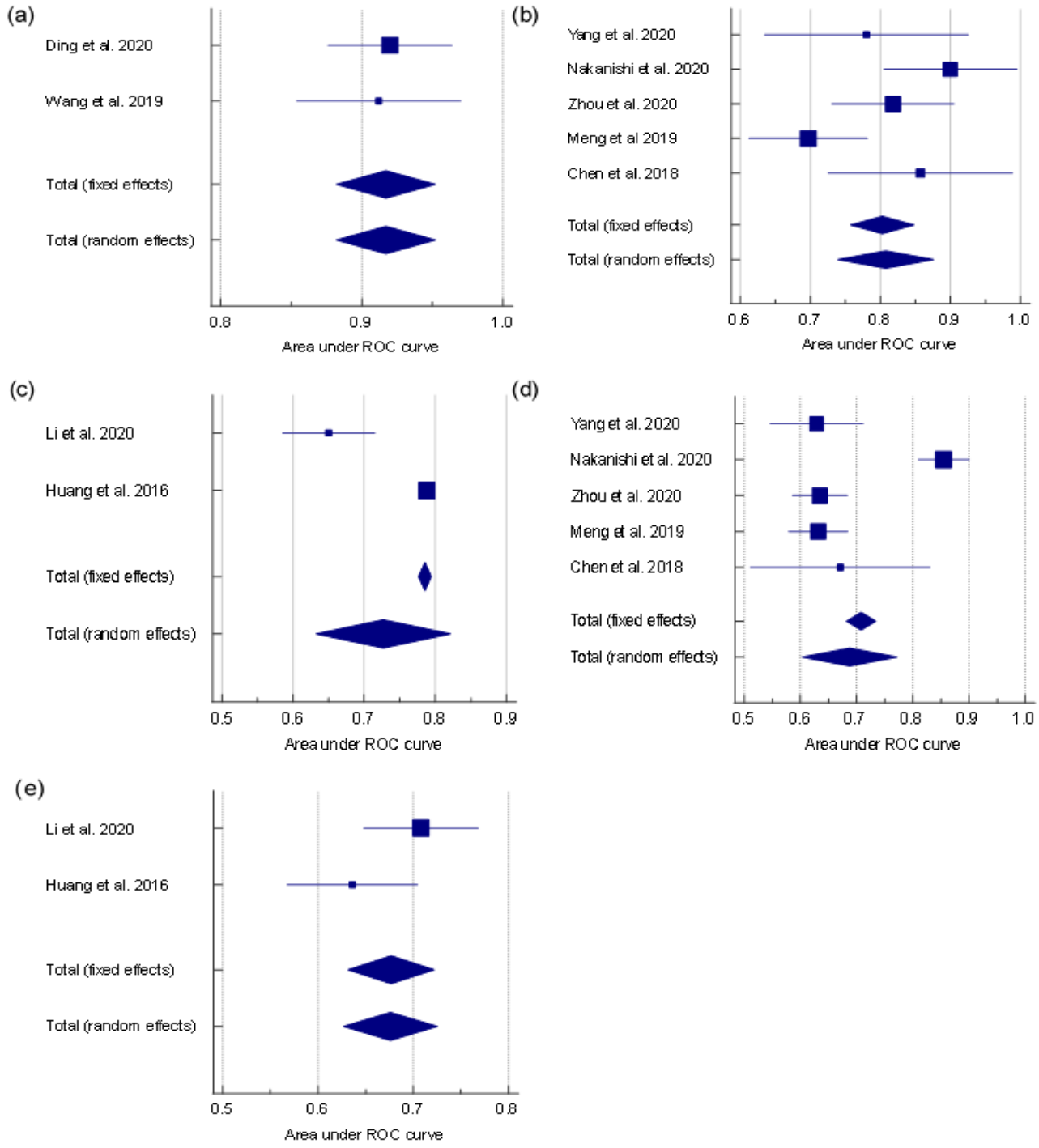

Figure. 12 Forest plots of per-patient area under the receiver operating characteristic curve (AUROC). (a) Deep learning in rectal cancer, (b) radiomics in rectal cancer, (c) radiomics in colorectal cancer, (d) radiologist in rectal cancer and (e) radiologist in colorectal cancer.

4.5 Discussion

To our knowledge, this is the first systematic review and meta-analysis of deep learning and radiomics performance in the assessment of lymph node metastasis in rectal and CRC patients. The results demonstrate a very high AUROC of 0.917 (95%CI, 0.882-0.952) when a deep learning model is used as a diagnostic tool compared with a radiomics model (AUROC 0.808, 95%CI 0.739-0.876). The diagnostic performance of both deep learning and radiomics models surpassed that of the radiologist assessment with an AUROC of 0.688 (95%CI, 0.603 to 0.772).

A number of research studies have already suggested AI has the potential to transform the healthcare sector particularly in areas where image recognition can be applied.[206-208] In terms of colorectal diseases, AI has been applied to colonic polyps, adenomas, colorectal cancer, ulcerative colitis and intestinal motility disorders.[209-212] Owing to the rapid development of AI technology, AI is bound to continually play an important role in the field of colorectal diagnosis and treatment.[213] Furthermore, the increase in computing power paired with the availability of large imaging databases offer the opportunity to develop more accurate AI algorithms.(10) At present, applications of deep learning to medical imaging are in vogue. However, deep learning models have several drawbacks, including variability in the images, large sample size, poor generalization and extensive computing resources. These models tend to rely on superficial data patterns and often fail when external factors such as different imaging acquisition parameters and types of scanners cause a distribution shift. [214]

In this review, most studies used radiomics (n=12), rather than deep learning methodology (n=5) largely owing to deep learning technology being more recent, but also because it requires specific expertise. This limits the ability to draw definitive comparisons between the two AI models as one is somewhat over-represented in the data. Additionally, most studies were retrospective in design, making them prone to confounding and selection bias. Several studies focused on the technical

aspects of the algorithm and did not address key limitations such as input variation, absence of clinical information (age, tumour site, patient history) and potential data overfitting often caused by noise in the data, overcomplicated models, and small sample sizes. Another issue, particularly common in deep learning studies, is the failure to report contingency tables or sufficient detail to enable reconstruction. We had to exclude five (29%) studies from the meta-analysis due to incomplete data. Most studies were conducted at a single-center and used internal verification or resampling methods (cross validation). Internal validation, however, tends to overestimate the AUROC due to the model's lack of generalizability, limiting the integration of AI models into the clinical setting.[215] Therefore, external validation prediction models using images from different hospitals are required to create reliable estimates on the level of performance at other sites.[216] The number of studies diagnosing lymph node metastasis on a per-nodal basis in this meta-analysis is small. This is understandable, given that lymph node metastasis is staged on a per-patient basis in the clinical setting. Interestingly, five studies on rectal cancer extracted radiomics features from CT despite MRI being the gold standard imaging modality for lymph node detection in clinical practice.

This meta-analysis has some limitations that merit consideration. Firstly, a relatively small number of deep learning studies were available for inclusion. This, along with the heterogeneity seen in radiomics studies, means that the summary estimates of AUROCs have to be interpreted with caution. Secondly, because of incomplete reporting of results by several studies, estimates of diagnostic performance were calculated using limited data. Thirdly, given the majority of the included studies originate from China, there is a potential for geographical bias. Lastly, the wide range of scanner types, imaging protocols, and criteria for lymph node metastasis used may have affected accuracy of results. Results for radiomics and the radiologist assessment were highly heterogenous, which may be attributed to the different imaging modalities and small sample sizes. In the future, diagnostic AI models will have to be rigorously evaluated on their clinical benefit in comparison to current standard of care, as not all are suitable for clinical practice. Therefore, studies

comparing AI with the clinicians' performance are most valuable and are more likely to ensure safe and effective implementation of AI technology into daily practice.[217,218]

4.6 Conclusion

AI models have the potential to predict lymph node metastasis more accurately on a per-patient basis in colorectal cancer than the radiologists' assessment, however, radiomics studies are heterogeneous and deep learning studies are scarce. With further development and refinement, AI models capable of accurately predicting nodal stage may represent a significant advance in pre-operative staging of colorectal cancer to better inform clinician and patient.

CHAPTER 5: A PROSPECTIVE STUDY OF DIAGNOSTIC ACCURACY OF MULTIDISCIPLINARY TEAM AND RADIOLOGY REPORTING OF PRE-OPERATIVE COLORECTAL CANCER LOCAL STAGING.

Statement of Authorship

Title of Paper	A prospective study of diagnostic accuracy of multidisciplinary team and radiology reporting of preoperative colorectal cancer local staging.
Publication Status	Published
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Name of Principal Author (Candidate)	Sergei Bedrikovetski		
Contribution to the Paper	Conception and design of the work Data acquisition Analysis and interpretation of data Drafting the final manuscript		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	01/08/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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5.1 Abstract

Introduction: The aim of this study was to correlate and assess diagnostic accuracy of preoperative staging at Multidisciplinary Team Meeting (MDT) against the original radiology reports and pathological staging in colorectal cancer patients.

Methods: A prospective observational study was conducted at two institutions. Patients with histologically proven colorectal cancer and available preoperative imaging were included. Preoperative tumour and nodal staging (cT and cN) as determined by the MDT and the radiology report (CT and/or MRI) were recorded. Kappa statistics were used to assess agreement between MDT and the radiology report for cN staging in colon cancer, cT and cN in rectal cancer, and Tumour Regression Grade (TRG) in patients with rectal cancer who received neoadjuvant therapy. Pathological report after surgery served as the reference standard for local staging, and AUROC curves were constructed to compare diagnostic accuracy of the MDT and radiology report.

Results: A total of 481 patients were included. Agreement between MDT and radiology report for cN stage was good in colon cancer (k=0.756, CI95% 0.686-0.826). Agreement for cT and cN and in rectal cancer was very good (kw=0.825, CI95% 0.758-0.892) and good (kw=0.792, CI95% 0.709-0.875), respectively. In the rectal cancer group that received neoadjuvant therapy, agreement on TRG was very good (kw=0.919, CI95% 0.846-0.993). AUROC curves using pathological staging indicated no difference in diagnostic accuracy between MDT and radiology reports for either colon or rectal cancer.

Conclusion: Preoperative colorectal cancer local staging was consistent between specialist MDT review and original radiology reports, with no significant differences in diagnostic accuracy identified.

5.2 Introduction

Colorectal cancer is the third most frequently diagnosed cancer in the world, with 1.9 million new cases in 2020. It is also the second leading cause of cancer-related death, accounting for an estimated 935,000 deaths annually.[1] Modern preoperative radiologic staging modalities, such as Computer Tomography (CT) and Magnetic Resonance Imaging (MRI), allow for fairly accurate pre-operative staging, and inform selection of the most appropriate management strategy for each patient.

In rectal cancer, pelvic MRI preoperative staging provides essential information on tumour depth infiltration and perirectal nodal metastasis.[219] These factors determine the need for neoadjuvant therapy and extent of surgical treatment. The role of preoperative CT imaging in colon tumours is to identify adjacent organ infiltration (T4b stage) and distant metastasis. Locoregional staging (T and N stage) is of marginal clinical utility given neoadjuvant therapy is not standard of care.[220] However, there is growing interest in administering neoadjuvant chemotherapy to decrease the risk of disease recurrence in locally advanced colon cancers.[17] In view of this, accurate preoperative staging for both colon and rectal cancer assists patient selection for neoadjuvant therapy and surgical planning.[11]

Most colorectal cancer guidelines state that all patients should be discussed at a Multidisciplinary Team Meeting (MDT);[221,222] a collaborative forum for decision making attended ideally by surgeons, radiologists, pathologists, and medical and radiation oncologists.[223] At the MDT, accurately documented preoperative staging assists decision making.[224] In rectal cancer, for instance, discussion in the MDTs have shown to increase the proportion of patients receiving neoadjuvant treatment, resulting in better local disease control and higher curative surgery rates.[225,226]

Previous studies in this field have shown inconsistencies in staging documentation and demonstrated that preoperative staging accuracy with MDT recommendation to be significantly higher compared to the radiology report alone.[227,228] However, most reports come from small and single-centre retrospective studies. Prospective data on the agreement and accuracy of MDT and radiology report in colorectal cancer are lacking, and in our context, with high quality specialised colorectal cancer staging reporting, it remains unclear whether the MDT discussion was upgrading or downgrading patient stage. Therefore, we aimed to prospectively investigate the level of agreement in preoperative staging between MDTs and radiology reports and to determine the accuracy of these modalities for diagnostic decision making in colorectal cancer.

5.3 Materials and methods

This prospective cohort study is reported according to the STARD statement[229] and was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (HREC/19/CALHN/73) and the Ethics Committee of a private tertiary care center (#116). This study was conducted in accordance with the Helsinki Declaration. The requirement for informed consent was waived given the low or negligible risk to patients.

5.3.1 Patient selection

Consecutive patients with histologically proven colon or rectal adenocarcinoma at two tertiary care centers (both in Adelaide, Australia) who were discussed at the weekly colorectal MDTs between March 1st 2019, and March 04th 2022, were considered for the study. Patients without available reports from CT/MRI of preoperative stages from MDT and radiology or cases where the reporting radiologist was also a member of the colorectal MDT were excluded.

5.3.2 Imaging and pathological evaluation

Preoperative imaging for colon and rectal cancer included abdominopelvic CT with oral and intravenous contrast or water as a negative contrast. Rectal cancers underwent high resolution multiparametric MRI. Rectal cancer patients receiving neoadjuvant therapy underwent restaging MRI 8-10 weeks following completion of their chemoradiotherapy.[21,230] All scans were reported by a specialist radiologist or junior radiologist supervised by a specialist radiologist at both institutions prior to MDT discussion. Reporting was performed in a standardised manner using the Cancer Council Australia recommended proforma.[231] Staging at MDT was determined by one of three specialist radiologists with specific experience in gastrointestinal and pelvic MRI and oncologic imaging, colorectal surgeons, medical and radiation oncologists, and pathologists. At the MDT meeting, CT or MRI scans were reviewed against the radiology report by specialist radiologists in combination with the treating team. Patients were recorded as node negative during data collection if there was no mention of abnormal nodes in the radiology report. Tumours above the peritoneal reflection were defined as colon cancers. Agreement of preoperative staging and restaging Tumour Regression Grade (TRG)[232] between MDT and radiology report for rectal cancer was also assessed. As previous studies have described[227,233], patients with rectal cancer were divided into "early surgery" or "neoadjuvant therapy" subgroups. The early surgery group underwent surgery after diagnosis or received short-course radiotherapy without a wait period (thus had pathological staging that could be used as the reference standard). The neoadjuvant therapy group received Total Neoadjuvant Therapy (TNT), or standard long course Chemoradiotherapy (CRT), or short course radiotherapy with a wait period (thus had significant tumour downstaging and the pathological staging could not be used to determine pre-operative clinical staging accuracy).

Tumours were grouped based on the presence or absence of tumour invasion through the muscularis propria into the surrounding mesorectum. Lymph node metastasis were defined as any visible node ≥ 9mm on the short axis, nodes with mucinous signal characteristics, nodes 5-9mm with two

additional morphologically suspicious features (round shape, irregular borders or heterogenous contrast enhancement) and nodes >5mm with all three features present were considered to be positive.[234] The presence of extramural vascular invasion (EMVI) was considered positive if tumour signal extends into an adjacent vascular structure from the primary tumour or involved lymph nodes, expanding and disrupting the vessel borders. A positive Circumferential Resection Margin (CRM) for upper and mid rectal tumours was defined as involvement of the mesorectal fascia or within 1mm of the mesorectal fascia. In low rectal tumours, tumour involving or within 1mm of inter-sphincteric plane or levator ani muscle was considered as involved CRM.[231] For colon cancer, MDT and radiology reported cN-stage were compared with the pN-stage. In the rectal cancer: early surgery group, MDT and MRI reported cT and cN-stage were compared with the pT and pN-stages. For imaging and pathological staging, the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging was used.[26]

5.3.3 Statistical analysis

Descriptive statistics were used to describe baseline characteristics. Agreement between MDT and radiology report for clinical colon cancer Nodal (cN) staging was evaluated using Cohen's kappa (k). A weighted Cohen's Kappa (kw) was applied for matrices larger than 2x2 quadratic in the agreement evaluation for clinical Tumour stage (cT), cN staging, CRM and EMVI for all rectal cancers, and radiological TRG (TRG 1-5) criteria proposed by Patel et al.[235] on restaging for the neoadjuvant therapy subgroup. A kappa and weighted-kappa values of <0.20 was considered 'Poor', 0.21–0.40 as 'Fair', 0.41–0.60 as 'Moderate', 0.61–0.80 as 'Good', and 0.81–1.00 as 'Very good'.[236] The Fisher's exact test was used for statistical analysis. Alpha was set at $p<0.05$. Diagnostic measures using pathological were assessed using Area Under the Receiver Characteristic Curve (AUROC), accuracy, sensitivity, specificity, Positive Predicted Value (PPV) and Negative Predicted Value (NPV). SPSS Statistics for Windows, version 27 (SPSS Inc.,

Chicago, Ill., USA) and MedCalc for Windows, version 16.4.3 (MedCalc Software, Ostend, Belgium) were used for analysis.

5.4 Results

5.4.1 Baseline Characteristics

A total of 481 patients were included (Figure. 13). Junior radiologists overseen by a specialist radiologist reviewed the scans of 151 (31%) patients, the remaining 330 (69%) patients had their scans reviewed by a specialist radiologist. The median age was 70 years (range 29-95) and 58% were male. Of these patients, 346 (72%) presented with colon cancer and 135 (28%) with rectal cancer. In rectal cancer, 55 (41%) received TNT, 10 (7%) received long-course CRT, 12 (9%) received short-course radiotherapy and 58 (43%) did not receive neoadjuvant treatment. The median number of resected lymph nodes for all resections was 18 (range, 1-124). Other demographics are summarized in Table 10.

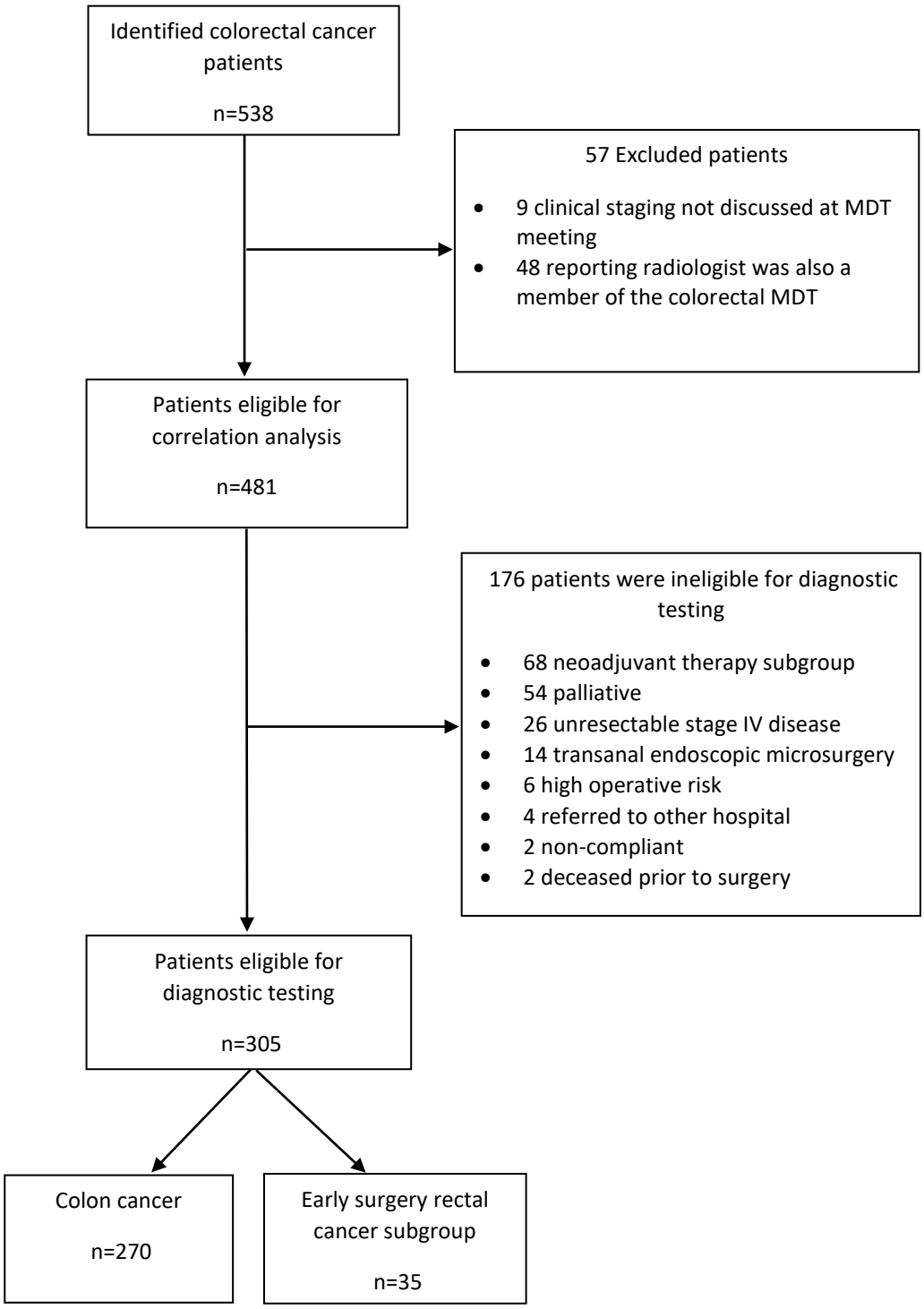

Figure. 13 Patient selection.

Table 10 Baseline characteristics of colorectal cancer patients	
Variable	**Value**
Age, median (range), y	70 (29-97)
Sex, n (%)	
Male	281 (58)
Female	200 (42)
Tumour location	
Caecum	49 (10)
Ascending colon	73 (15)
Transverse colon	88 (18)
Descending colon	19 (4)
Sigmoid colon	117 (24)
Rectum	135 (28)
Neoadjuvant therapy †, n (%)	
TNT	55 (41)
Long course CRT	10 (7)
Short course RT	12 (9)
None	58 (43)
Operation	
Extended/Right hemicolectomy	153 (44)
Left hemicolectomy	8 (2)
Subtotal or total colectomy	19 (6)
High anterior resection	66 (19)
Low anterior resection	20 (6)
Ultra-low anterior resection	20 (6)
Hartmann's operation	32 (9)
Abdominoperineal resection	10 (3)
Proctocolectomy	3 (1)
Pelvic exenteration	12 (4)
Ileocolic resection	2 (1)
No. of harvested LNs	18 (1-124)
No. of positive LNs	0 (0-31)

TNT, total neoadjuvant therapy; CRT, chemoradiotherapy; RT, radiotherapy; LNs, lymph nodes

† Rectal cancer only

5.4.2 Agreement between MDT and radiology report

In 346 colon cancer patients, agreement between MDT and radiology report for cN stage was good (k=0.756, CI95% 0.686-0.826, p<0.001). In 135 rectal cancer patients (total cohort), agreement for cT and cN was very good (kw=0.825, CI95% 0.758-0.892, p<0.0001) and good (kw=0.792, CI95% 0.709-0.875, p<0.0001), respectively. In addition, the agreement for CRM and EMVI was very good (k=0.920, CI95% 0.851-0.989, p<0.0001) and very good (k=0.814, CI95% 0.740-0.914, p<0.0001), respectively. Out of 68 patients in the neoadjuvant therapy subgroup, 64 patients underwent re-staging MRI. The correlation of TRG between MDT and radiology report was very good (kw=0.919, CI95% 0.846-0.993, p<0.0001).

5.4.3 Diagnostic accuracy: cN stage in colon cancer

Diagnostic measures were calculated for 270 colon cancer patients with available histopathology (Table 11, Figure. 14). The AUROC showed no significant difference between the MDT and radiology report (0.667 vs. 0.667, p=1.00). The MDT had similar accuracy (69% vs. 70%), sensitivity (56% vs. 52%), PPV (63% vs. 65%) and specificity (78% vs. 81%) compared with the radiology report. The NPV was 72% in both the MDT and radiology report.

Table 11 Diagnostic results of MDT and CT report compared with pathological N staging for colon cancer

N-stage	**pN**		**P-value**
MDT cN	**pN0**	**pN1-2**	
cN0	126	48	<0.0001
cN1-2	36	60	
Report cN			
cN0	132	52	<0.0001
cN1-2	30	56	
	MDT cN	**Report cN**	
AUROC	0.667 (95%CI 0.607-0.723)	0.667 (95%CI 0.607-0.723)	1.00
Accuracy (%)	69 (95%CI 63-74)	70 (95%CI 64-75)	
Sensitivity (%)	56 (95%CI 46-65)	52 (95%CI 42-62)	
Specificity (%)	78 (95%CI 71-84)	81 (95%CI 75-87)	
PPV (%)	63 (95%CI 54-70)	65 (95%CI 56-73)	
NPV (%)	72 (95%CI 68-77)	72 (95%CI 67-76)	

MDT, multidisciplinary team meeting; AUROC, area under the receiver operating characteristic curve, PPV, positive predictive value; NPV, negative predictive value.

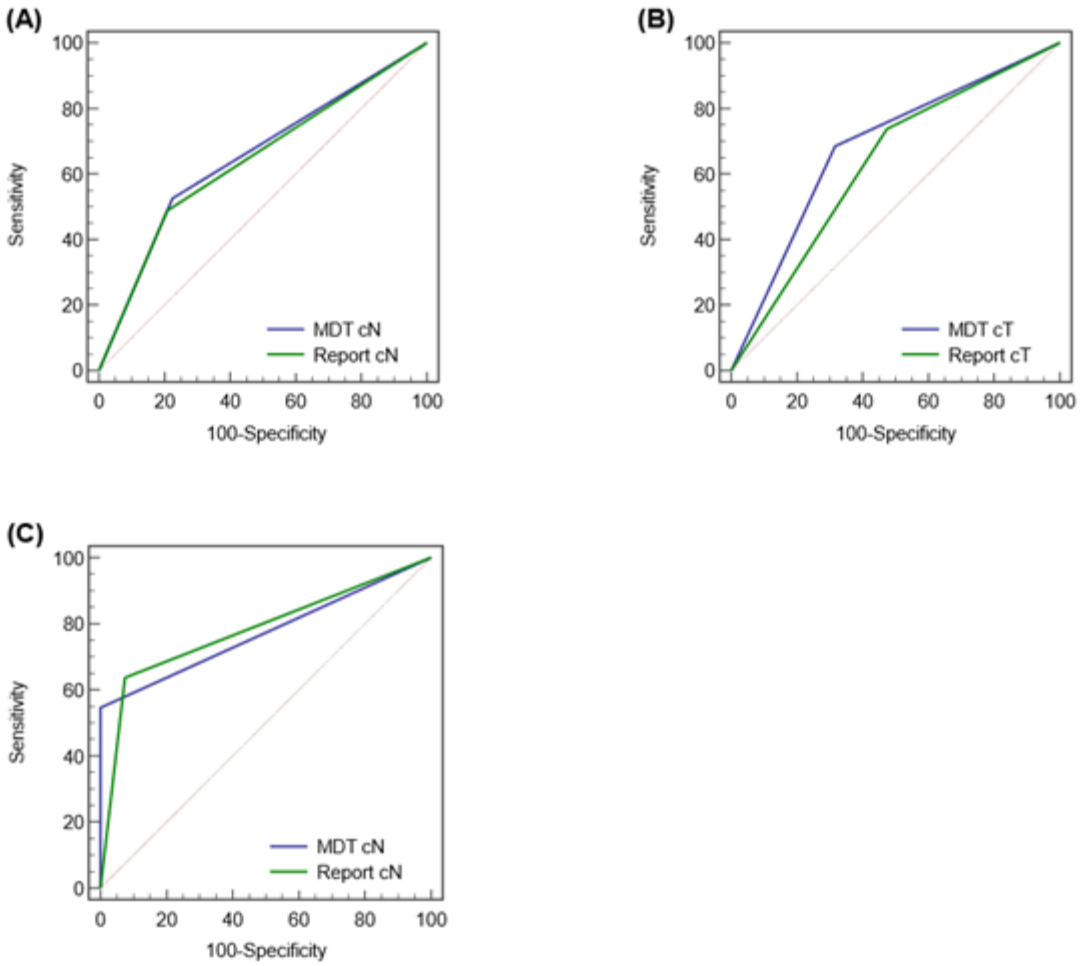

Figure. 14 Receiver operating characteristic (ROC) curves comparing staging at MDT versus radiology report for (A) N stage in the colon cancer, (B) T-stage in the rectal cancer early surgery subgroup, (C) N-stage in the rectal cancer early surgery subgroup.

5.4.4 Diagnostic accuracy: cT and cN in early surgery rectal cancer subgroup

Diagnostic measures were calculated for 35 early surgery rectal patients (Table 12, Figure. 14). MDT could differentiate low-risk (cT0-T2) from high-risk tumours (cT3-T4) with an 71% vs. 66% accuracy, 67% vs. 72% sensitivity, 76% vs. 59% specificity, 75% vs. 65% PPV, 68% vs. 67% NPV compared to the radiology report. The AUROC was not significantly different (AUROC 0.716 vs. 0.655, p=0.273). The MDT differentiated between node positive (cN1-2) from node negative (cN0) tumours with an 77% vs. 74% accuracy, 45% vs. 55% sensitivity, 92% vs. 83% specificity, 71% vs. 60% PPV, 79% vs. 80% NPV, compared to the radiology report. The AUROC was not significantly different (AUROC 0.686 vs. 0.689, p=0.944).

Table 12 Accuracy of clinical report and MDT tumour staging versus pathologic tumour stage in the early surgery subgroup for rectal cancer

T stage	**pT**		**P Value**
MDT cT	**T0-2**	**T3-4**	
cT0-2	13	6	0.018
cT3-4	4	12	
Report cT			
cT0-2	10	5	0.068
cT3-4	7	13	
N Stage	**pN**		
MDT cN	**N0**	**N1-2**	
cN0	22	6	0.021
cN1-2	2	5	
Report cN			
cN0	20	5	0.041
cN1-2	4	6	
	MDT cT	**Report cT**	
AUROC	0.716 (95%CI 0.538-0.855)	0.655 (95%CI 0.476-0.807)	0.273
Accuracy (%)	71 (95%CI 54-85)	66 (95%CI 48-81)	
Sensitivity (%)	67 (95%CI 41-87)	72 (95%CI 47-90)	
Specificity (%)	76 (95%CI 50-93)	59 (95%CI 33-82)	
PPV (%)	75 (95%CI 55-88)	65 (95%CI 50-78)	
NPV (%)	68 (95%CI 52-81)	67 (95%CI 46-82)	
	MDT cN	**Report cN**	
AUROC	0.686 (95%CI 0.507-0.831)	0.689 (95%CI 0.511-0.834)	0.944
Accuracy (%)	77 (95%CI 60-90)	74 (95%CI 57-88)	
Sensitivity (%)	45 (95%CI 17-77)	55 (95%CI 23-83)	
Specificity (%)	92 (95%CI 73-99)	83 (95%CI 63-95)	
PPV (%)	71 (95%CI 36-92)	60 (95%CI 35-81)	
NPV (%)	79 (95%CI 68-86)	80 (95%CI 67-89)	

MDT, multidisciplinary team meeting; AUROC, area under the receiver operating characteristic curve, PPV, positive predictive value; NPV, negative predictive value.

5.5 Discussion

This is the first study to prospectively compare diagnostic agreement between a specialised colorectal cancer MDT and the radiology report for colorectal cancer patients. Our results demonstrate a good level of diagnostic agreement between MDT and radiology report in the setting of colorectal cancer, and no statistically significant difference in diagnostic accuracy.

In line with a meta-analysis and a Danish population-based study, we found that it remains challenging to correctly identify patients with nodal involvement. The meta-analyses of 13 studies found summary estimates for sensitivity and specificity concerning nodal involvement of 71% and 67%, respectively,[237] and the Danish study including 4834 patients found a sensitivity of 57%, specificity of 66% and an accuracy of 63% in predicting nodal involvement by the MDT.[238] Similar results are observed in the current study, with a 56% sensitivity, 78% specificity and 69% accuracy. A recent study by Koh et al., in which nodal staging was assessed by an expert radiologist issuing formal CT reports, found a sensitivity and specificity of 85% and 40%, respectively.[239] The differences in sensitivity and specificity between the current study and their findings can likely be attributed by their low sample size (n=23). Moreover, Hong et al. reported the radiologist diagnostic AUROC for malignant nodal status of 0.663 using the largest measured short-axis diameter of lymph node and presence of internal heterogeneity when combined.[240] Our results demonstrate a similar AUROC of 0.667 for colon cancer nodal involvement staged on MDT and radiology report. This diagnostic difficulty likely arises from CT being unable to detect micrometastasis and distinguishing benign node enlargement secondary to peritumoral inflammation from those with metastatic disease. Considering the limited clinical significance of preoperative nodal staging in colon cancer and the concordance between MDT review and the radiology report found in our study, preoperative nodal staging during MDT could be avoided. Nevertheless, it is clear that MDT is still to be recommended to make clinical management decisions in general, and perhaps less

focus on repeat nodal staging would increase MDT efficiency and allow more cases to be discussed with that goal in mind.

Preoperative rectal cancer staging is important for the choice of treatment and prognosis of the patient, as the cT and cN stage are key factors to determine whether a patient is best treated by immediate surgery or could benefit from neoadjuvant therapy first. In our study, the sensitivity, specificity and AUROC assessment of advanced T stage (T0-2 vs. T3-4) in the MDT (67% sensitivity, 76% specificity and AUROC 0.716) and radiology report (72% sensitivity, 59% specificity and AUROC 0.655) were lower than in the meta-analysis by Zhang et al. (pooled sensitivity 87%, specificity 73% and AUROC 0.918).[241] This disparity in diagnostic AUROCs could be due to the different interpretation of perirectal tissue invasion, which, as pointed out by Zhang, could have an effect on diagnostic accuracy. In comparison with retrospective data from Australia and New Zealand, the accuracy of extramural tumour involvement on MDT staging was higher in our cohort (71% vs. 51% vs. 52%). [143,242]

The diagnosis of mesorectal Nodal involvement (cN) by MDT and radiology report in the early surgery rectal cancer subgroup drew mixed results compared to the pooled results of radiologists' staging from Al-Sukhni et al. meta-analysis.[144] Our sensitivity on radiology reporting compares poorly to their pooled result (55% vs 77%), while our specificity for the radiology report is much higher that reported in this meta-analysis (83% vs 71%). Similarly, when comparing our MDT and radiology report results to those reported by Park et al., they reported a higher sensitivity (78%) and lower specificity (83%).[233] The sensitivity and specificity when adopting morphological and signal criteria to assess malignant nodes remains an area of controversy.[243-245] Nevertheless, our study and Park et al. both used size and nodal characteristics to identify suspicion of nodal metastasis. The poor sensitivity in our cohort could be attributed to a small sample size, selection bias in the early surgery subgroup and by a higher size criterion (nodal short-axis diameter) being applied by the

radiologist. Individual colorectal unit thresholds also matter for calibration. It maybe that due to the high adoption of TNT at the two hospitals in questions, identification of true negatives has taken on relatively more importance than identification of true positives.

There are several limitations to this study. Firstly, since rectal cancer patients with metastatic nodes undergo neoadjuvant treatment, selection bias is expected in the early surgery rectal cancer subgroup. Therefore, we are uncertain to what degree our findings can be generalized to patients with more advanced disease. Secondly, due to the small number of patients in the early surgery rectal cancer group, staging accuracy could not completely be assessed. Finally, given our small sample size, our findings need to be verified with a larger population study. MDT remains important for the discussion of management strategies and overall co-ordination of cancer care.

5.6 Conclusion

Preoperative colorectal cancer local staging was consistent between specialised MDT and original radiology reports, with no significant differences in diagnostic accuracy identified between MDT and the radiology report in nodal staging in colon cancer and tumour and nodal staging in the early surgery rectal cancer.

CHAPTER 6: DEEP LEARNING TO PREDICT LYMPH NODE STATUS ON PRE-OPERATIVE STAGING CT IN PATIENTS WITH COLON CANCER.

Statement of Authorship

Title of Paper	Deep learning to predict lymph node status on pre-operative staging CT in patients with colon cancer.
Publication Status	Submitted for Publication
Publication Details	Manuscript submitted to Clinical Imaging

Principal Author

Name of Principal Author (Candidate)	Sergei Bedrikovetski		
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Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	01/07/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Signature		Date	01/08/2022

6.1 Abstract

Introduction

Lymph Node (LN) metastases are an important determinant of survival in patients with colon cancer, but remain difficult to accurately diagnose on preoperative imaging. This study aimed to develop and evaluate a deep learning model to predict LN status on preoperative staging Computed Tomography (CT).

Methods

In this ambispective diagnostic study, a deep learning model using a ResNet-50 framework was developed to predict LN status based on preoperative staging CT. Patients with a preoperative staging abdominopelvic CT who underwent surgical resection for colon cancer were enrolled. Data were retrospectively collected from February 2007 to October 2019 and randomly separated into training, validation, and testing cohort 1. To prospectively test the deep learning model, data for testing cohort 2 was collected from October 2019 to July 2021. Diagnostic performance measures were assessed by the Area Under the Receiver Operating Characteristic Curve (AUROC).

Results

A total of 1201 patients (median [range] age, 72 [28-98 years]; 653 [54.4%] male) fulfilled the eligibility criteria and were included in the training (n=401), validation (n=100), testing cohort 1 (n=500) and testing cohort 2 (n=200). The deep learning model achieved an AUROC of 0.619 (95%CI 0.507-0.731) in the validation cohort. In testing cohort 1 and testing cohort 2 the AUROC was and 0.542 (95%CI 0.489-0.595) and 0.486 (95%CI 0.403-0.568), respectively.

Conclusion

A deep learning model based on a ResNet-50 framework does not predict LN status on preoperative staging CT in patients with colon cancer.

6.2 Introduction

Colon cancer is the fifth most diagnosed cancer amongst men and women worldwide. In 2020, over one million newly diagnosed cases and 576,858 deaths were attributed to this disease.[1] The standard curative treatment remains complete resection of the primary tumour with regional Lymph Nodes (LN) and adjuvant chemotherapy in higher risk patients.[246] The presence of LN metastasis is a vitally important determinant of prognosis and treatment options.[15,247] Currently, these LNs are examined by specialist pathologists, with decisions about adjuvant therapy only possible after resection in patients without distant metastatic disease.[248] In clinical practice, knowledge of preoperative LN involvement is rarely used given that neoadjuvant chemotherapy is typically only administered in patients with stage IV disease. Recently the Foxtrot trial revealed that neoadjuvant chemotherapy can be delivered safely with potential for pathological downstaging.[17] However, this study included patients with a wide range of colon cancer staging. The limited diagnostic accuracy of pre-operative LN staging currently precludes the possibility of stratifying patients for neoadjuvant treatment.

Computed Tomography (CT) is the most common imaging modality used in the preoperative staging of colon cancer. Despite excellent performance for the assessment of distant metastasis, the accuracy of preoperative assessment of LNs remains low; ranging from 54% to 64% using current diagnostic criteria based on size (LNs >1cm).[11,249,250] Several studies have attempted to apply different diagnostic criteria based on size, signal intensity, and morphology. However, the results of these studies are varied, and to date, there are no validated imaging criteria for the preoperative assessment of metastatic LNs.[237,251,252]

Artificial intelligence has demonstrated excellent diagnostic performance on preoperative LN staging in a variety of abdominopelvic malignancies.[187] Deep learning as a subset of artificial intelligence is emerging as a more effective way to extract information from medical images in

comparison with traditional models. Deep learning has the advantage of automatically and adaptively learning spatial hierarchies of features through its convolutional neural layers.[58] However, evidence regarding the use of deep learning for predicting LN staging in patients with colon cancer is scarce. Therefore, this study aimed to develop and evaluate a deep learning model to predict LN status on preoperative staging CT in patients with colon cancer.

6.3 Materials and methods

6.3.1 Study design

This ambispective diagnostic cohort study is reported using the Artificial Intelligence in Medical Imaging (CLAIM) guidelines.[253] The study protocol was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (HREC/19/CALHN/73) and St Andrew's Hospital Human Research Ethics Committee (#116). This study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was waived for all study participants.The goal of this study was to develop and evaluate a deep learning model used to predict LN status based on preoperative staging abdominopelvic CT in patients with colon cancer.

6.3.2 Data

Patients diagnosed with colonic adenocarcinoma who underwent surgical resection with regional lymphadenectomy treated/referred to the Royal Adelaide Hospital or St. Andrews Hospital, South Australia were eligible for inclusion. All included patients underwent standard unenhanced or contrast-enhanced CT preoperatively. As a result, some of the preoperative staging CT scans originated from the referring hospitals. The training cohort, validation cohort, and testing cohort 1 comprised of 401, 100, and 500 retrospectively included patients treated between February 2007 and October 2019, respectively. Testing cohort 2 comprised of 200 prospectively included patients treated between October 2019 and July 2021 with the same enrollment criteria. Exclusion criteria consisted of patients whose original CT scans were corrupted or not available, received neoadjuvant

chemotherapy, or had missing pathological N stage. Baseline clinicopathological data including age, sex, tumour location, procedure type, and pathological TNM stage were extracted from a prospectively collected colorectal cancer database.

6.3.3 Ground Truth

The ground truth for N stage was determined on pathology assessment of the surgical specimen. Staging was based on the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging criteria.[26]

6.3.4 CT image acquisition and processing

All patients underwent 0.5mm-7mm slice, standard unenhanced or post-intravenous contrast-enhanced preoperative CT of the abdomen and pelvis, with oral contrast or water as a negative contrast. We primarily analysed the portal venous phase CT images because of the clarity by which the LNs can be seen, however, we also analysed the few selected cases where only an arterial contrast-enhanced CT was available. A standard unenhanced CT was performed for patients with renal impairment or allergic to the intravenous contrast. Preoperative CT scans were exported from the Picture Archiving and Communication System (Carestream), or, through InteleViewer™ (Intelerad Medical Systems Inc) for CT scans performed in private imaging centers. Details regarding the CT systems are presented in Appendix C: Table 1. Axial plane sequences were isolated from the remainder of the CT images and anonymised using MicroDicom viewer (version 3.2.7; www.microdicom.com). Each axial plane CT sequence was assigned a binary label based on the ground truth (pN0 vs pN1-2).

Manual segmentation of regional LNs on axial slices was conducted by a science postgraduate student (S.B.) and a junior medical officer (W.S) trained and supervised by a senior colorectal surgeon (T.S.) who ensured the correct segmentation of the regional LNs during surgery using the

ITK-SNAP software (version 3.6.0; www.itksnap.org) (Appendix C: Figure. 1).[254] Regional LNs were segmented according to the anatomical location of the primary tumour. For right sided tumours, segmentation included the mesenteric LNs around the ileocolic vessels (blood supply to the cecum and proximal ascending colon), right colic vessels (blood supply to the mid-distal ascending colon), and middle colic vessels (blood supply to the proximal to the mid-transverse colon) arising from the superior mesenteric vessels. For left-sided tumours, mesenteric LNs were segmented around the left colic vessels (blood supply to the distal third of the transverse colon, the splenic flexure, and descending colon) and sigmoid vessels (blood supply to the sigmoid colon) arising from the inferior mesenteric vessels. Manual LN segmentation was performed in the training and validation cohorts (n=501) (Appendix C: Table 2).

6.3.5 Deep learning model

We proposed a convolutional neural network consisting of a segmentation ResNet-50 model and a classification ResNet-50 model to predict LN metastasis based on CT imaging.[255] The ResNet-50 model consisted of 48 convolution layers, 1 MaxPool, and 1 Average Pool layer. In the segmentation task, the ResNet-50 (Figure. 15) was used as the encoder of the segmentation model, and the several transposed convolutions were followed by the residual blocks in the decoder (Figure. 16). We used the bilinear interpolation in the last layer to restore the feature map to the original resolution. The segmentation model played an assistant role in classification. We used the segmentation model to predict the positive slices in each volume which would be inputted into the classification model for diagnosis. The backbone (encoder) of the segmentation model was used to initialize the classification model. The ResNet-50 model, which has the same architecture as the segmentation encoder, was used in the classification task. The backbone was initialized by using the segmentation pre-trained weights. The pre-trained segmentation model was utilised for each volume to segment lymph nodes and select 40 slices as the candidates for diagnosis. These candidates shared the same semantic label as the volume. The classification model took these slices as input to

make the final decision. We used the binary cross-entropy loss to optimize the classification model (Figure. 17).

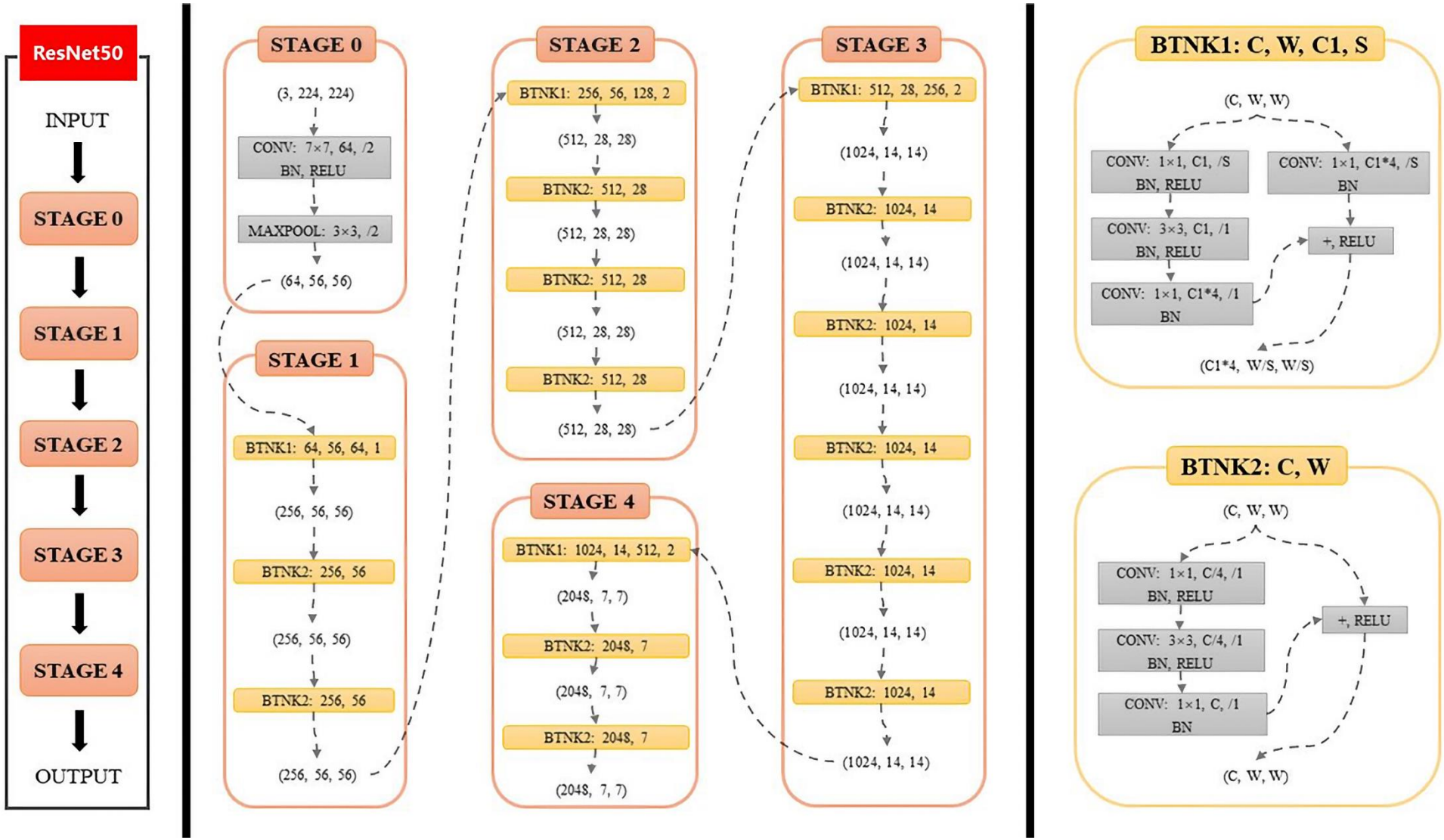

Figure. 15 ResNet-50

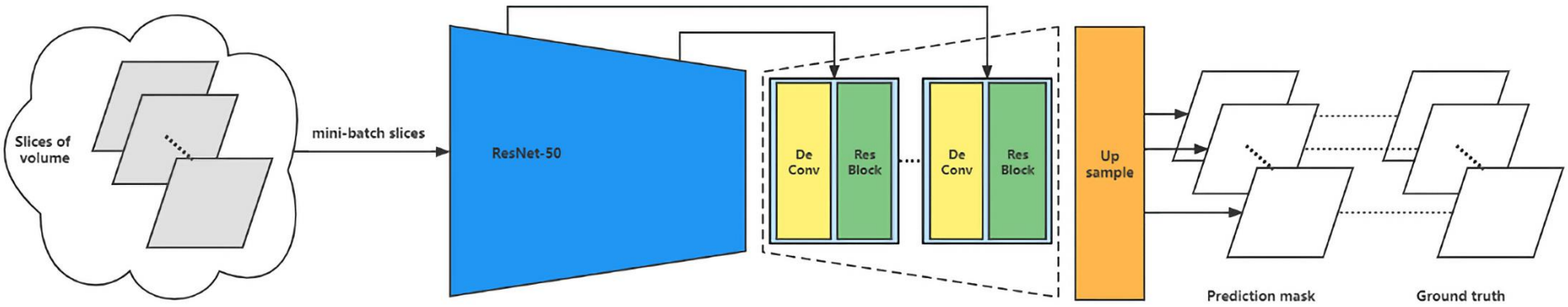

Figure. 16 Segmentation model

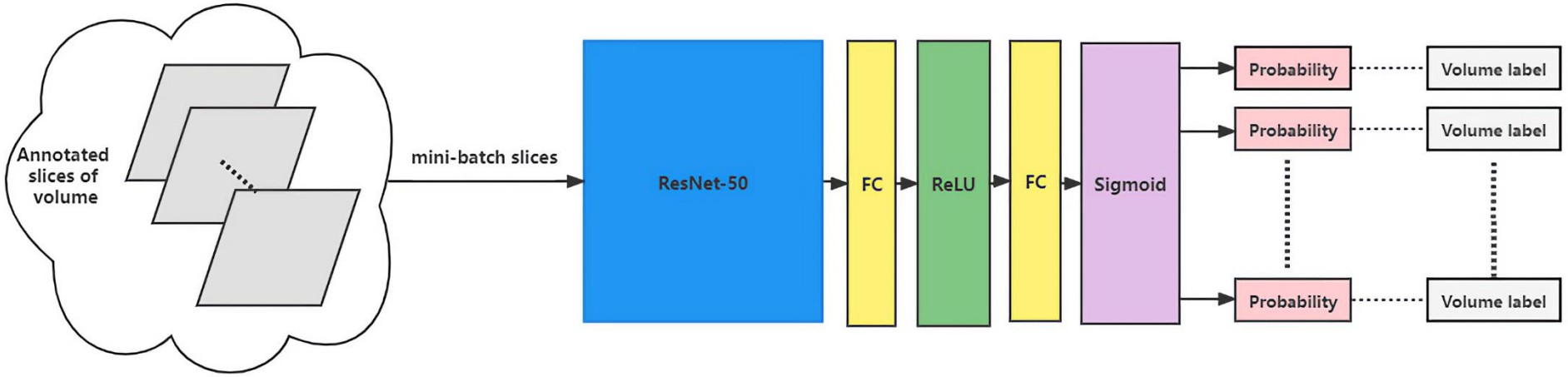

Figure. 17 Classification model

6.3.6 Performance evaluation

The prediction model was assessed by measuring the Area Under the Receiver Operating Characteristic curve (AUROC), accuracy, sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV).

6.3.7 Statistical analysis

The parametricity of continuous measures was determined using the Shapiro-Wilk test. Normally distributed data were expressed as mean (standard deviation) and nonparametric data as median (range). Categorical measures were presented as frequencies and percentiles. A comparison of groups was performed using Pearson's chi-squared test concerning categorical data. Exact or Monte Carlo methods were used for calculations depending on the table type and data count. One-way ANOVA or Kruskal-Wallis test was performed with respect to continuous data. A P value less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Macintosh, version 28 (IBM Corp., Armonk, N.Y., USA) and MedCalc for Windows, version 20.027 (MedCalc Software, Ostend, Belgium).

6.4 Results

6.4.1 Baseline characteristics

A total of 1201 patients (median (range) age, 72 (28-98) years; 653 (54.4%) male) were included in the study (Figure. 18). The clinicopathological characteristics for the training cohort (n=401), validation cohort (n=100), training cohort 1 (n=500) and testing cohort 2 (n=200) are listed in Table 13. A significant difference was found between gender, tumour location, operation, pathological T stage and N stage, the total number of LN harvested, and the total number of positive LNs. A significant difference was also found in the types of scanners and the thickness of CT scan slices (Supplementary Table S1-2).

Table 13 Clinicopathological characteristics of patients with colon cancer					
Variables	**Training Cohort (n=401)**	**Validation Cohort (n=100)**	**Testing Cohort 1 (n=500)**	**Testing Cohort 2 (n=200)**	**P-value**
Age, median (range), y	74 (28-97)	75 (30-91)	71 (29-98)	72 (29-94)	0.26
Gender					**0.03**
Male	241 (60.1)	54 (54.0)	251 (50.2)	107 (53.5)	
Female	160 (39.9)	46 (46.0)	249 (49.8)	93 (46.5)	
Tumor location					**<0.001**
Right	222 (55.4)	83 (83.0)	302 (60.4)	118 (59.0)	
Left	179 (44.6)	17 (17.0)	198 (39.6)	82 (41.0)	
Operation					**<0.001**
Right hemicolectomy	186 (46.4)	43 (43.0)	237 (47.4)	91 (45.5)	
Extended right/transverse colectomy	32 (8.0)	29 (29.0)	56 (11.2)	22 (11.0)	
Left hemicolectomy	12 (3.0)	5 (5.0)	12 (2.4)	3 (1.5)	
HAR	130 (32.4)	8 (8.0)	148 (29.6)	48 (24.0)	
Hartmann's	9 (2.2)	3 (3.0)	12 (2.4)	15 (7.5)	
Subtotal or total colectomy	26 (6.5)	10 (10.0)	34 (6.8)	16 (8.0)	
Proctocolectomy	5 (1.2)	0 (0.0)	1 (0.2)	2 (1.0)	
Other [a]	1 (0.2)	2 (2.0)	0 (0.0)	3 (1.5)	
pT stage					**0.003**
T0/Tis	8 (2.0)	2 (2.0)	17 (3.4)	4 (2.0)	
T1	49 (12.2)	8 (8.0)	59 (11.8)	26 (13.0)	
T2	36 (9.0)	5 (5.0)	83 (16.6)	20 (10.0)	
T3	220 (54.9)	55 (55.0)	244 (48.8)	94 (47.0)	
T4	88 (21.9)	30 (30.0)	97 (19.4)	56 (28.0)	
pN stage					**0.004**
N0	261 (65.1)	47 (47.0)	324 (64.8)	117 (58.5)	
N1/2	140 (34.9)	53 (53.0)	176 (35.2)	83 (41.5)	
Total no. of LNs harvested, median (range)	16 (1-154)	18 (1-60)	18 (1-51)	20 (1-124)	**<0.001**
No. of positive LNs, median (range)	0 (0-18)	1 (0-32)	0 (0-18)	0 (0-12)	**0.001**

LNs, Lymph nodes; HAR, high anterior resection

Data are presented as number (percentage) of patients unless otherwise indicated.

[a] Other: ileocolic resections and total pelvic exenterations

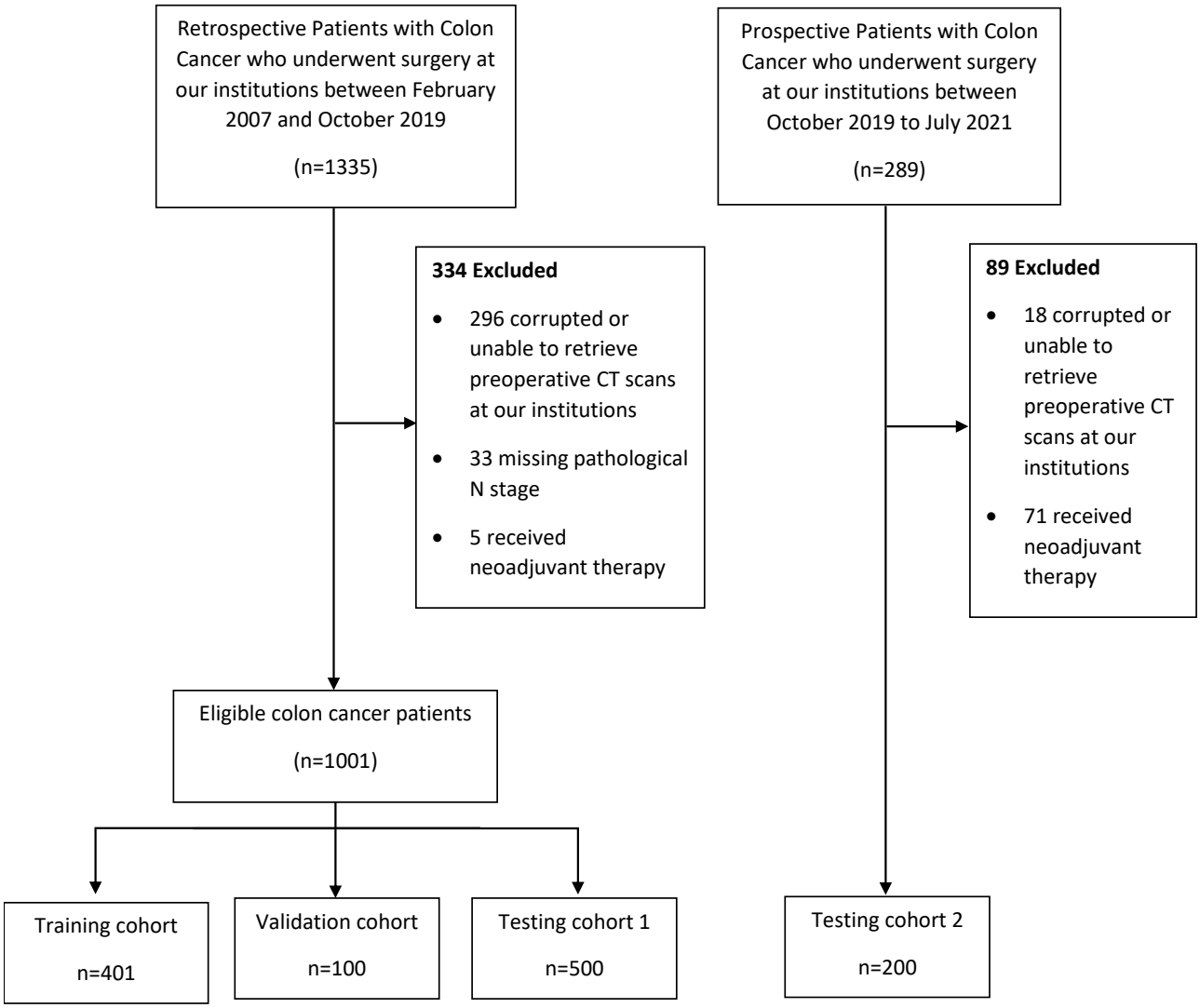

Figure. 18 Patient selection

6.4.2 Performance of the deep learning model

In the validation cohort, the deep learning model achieved an AUROC of 0.619 (95%CI 0.507-0.731) (Figure. 19). The deep learning model achieved a 96.2% (95%CI 87.0-99.5) sensitivity, 12.8% (95%CI 48.3-25.7) specificity, 57.0% (95%CI 46.7-66.9) accuracy, 55.4% (95%CI 52.4-58.4) PPV and 75.0% (38.9-93.4) NPV. For testing, the deep learning model yielded AUROC values of 0.542 (95%CI 0.489-0.595) in testing cohort 1 and 0.486 (95%CI 0.403-0.568) in testing cohort 2. The deep learning model showed high sensitivities of 96.6% (95%CI 92.7-98.7) and 91.6% (95%CI 83.4-96.5), low specificities of 5.2% (95%CI 3.1-8.3) and 6.0% (95%CI 2.4-11.9) and low accuracies of 37.4% (95%CI 33.1-41.8) and 41.5% (95%CI 34.6-48.7) in the testing cohort 1 and testing cohort 2, respectively. Of note, the model had PPVs of 35.6% (95%CI 34.8-36.5) and 40.9% (95%CI 39.0-42.8) and NPVs of 73.9% (95%CI 53.2-87.6) in the 2 testing cohorts, respectively (Table 14).

Table 14 Diagnostic performance of the LN metastasis model for the assessment of LN metastasis in the validation and testing cohorts

Cohort	**AUROC (95%CI)**	**Accuracy (95%CI)**	**Sensitivity (95%CI)**	**Specificity (95%CI)**	**PPV (95%CI)**	**NPV (95%CI)**
Validation cohort	0.619 (0.507-0.731)	57.0 (46.7-66.9)	96.2 (87.0-99.5)	12.8 (48.3-25.7)	55.4 (52.4-58.4)	75.0 (38.9-93.4)
Testing cohort 1	0.542 (0.489-0.595)	37.4 (33.1-41.8)	96.6 (92.7-98.7)	5.2 (3.1-8.3)	35.6 (34.8-36.5)	73.9 (53.2-87.6)
Testing cohort 2	0.486 (0.403-0.568)	41.5 (34.6-48.7)	91.6 (83.4-96.5)	6.0 (2.4-11.9)	40.9 (39.0-42.8)	50.0 (26.7-73.3)

AUROC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value

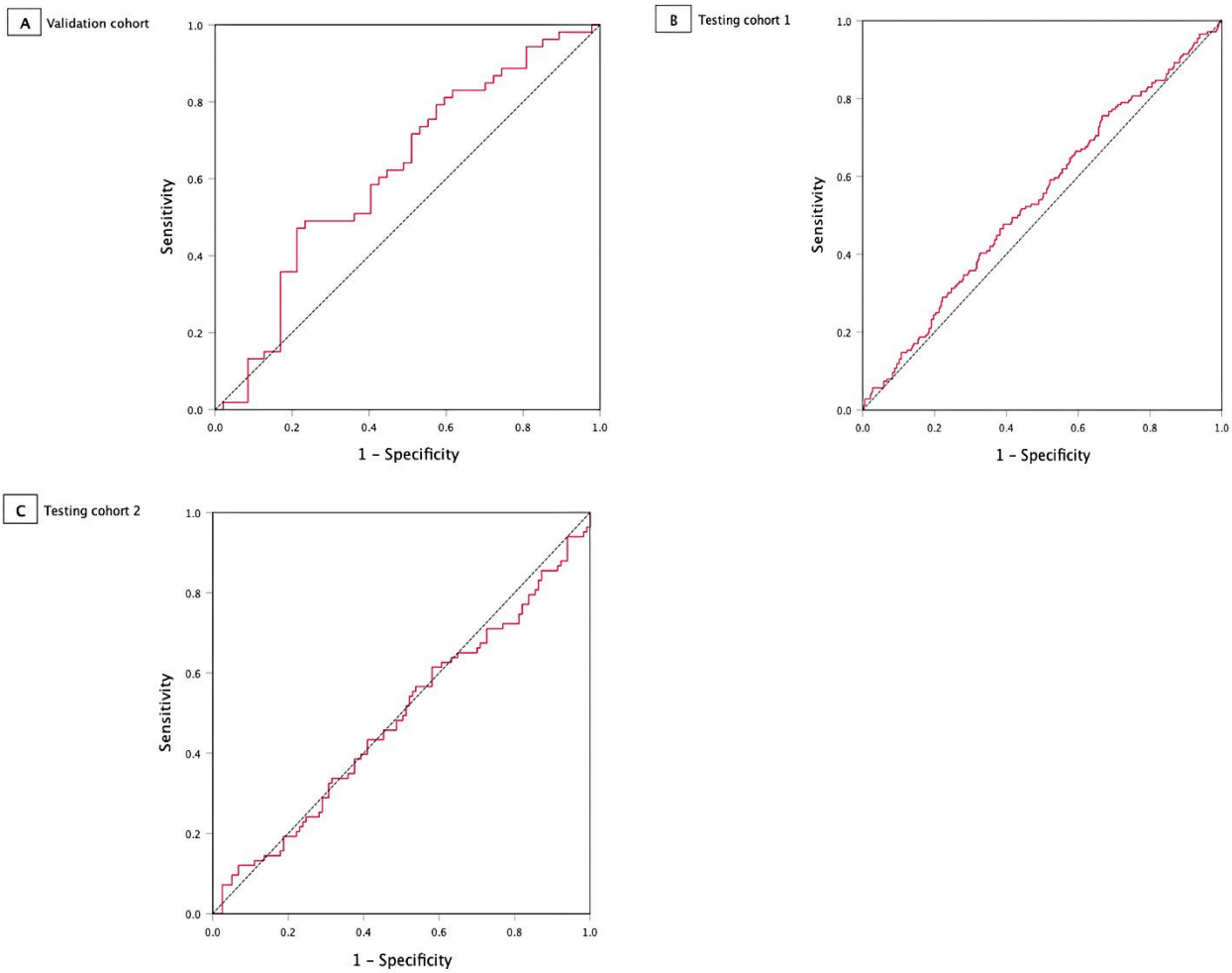

Figure. 19 The Area Under the Receiver Operating Characteristic Curves (AUROCs) derived from the deep learning model for lymph node staging in the validation and 2 training cohorts.

6.5 Discussion

In this ambispective diagnostic study, we attempted to develop a deep learning model to predict LN status on preoperative staging CT in patients with colon cancer. Our deep learning model showed a low predictive ability and reproducibility across validation and two different testing cohorts. Moreover, while the model had high sensitivity, it had very low specificity for malignant lymph nodes. To our knowledge, this is the largest diagnostic study to use deep learning for the prediction of LN staging on preoperative CT imaging for patients with colon cancer.

Recently, two meta-analyses have shown that most artificial intelligence models used to predict LN staging in colorectal cancer are radiomics-based signatures.[187,256] However, this approach relies on predefined handcrafted features that carry inherent observer bias which may cause relevant information contained in the image to be missed or removed.[46] Consequently, we developed a deep learning model to try to overcome this problem by automatically learning from LN segmentations and CT images, a model that might uncover subtle relations between LNs characteristics and metastatic potential.[52,257]

Somewhat surprisingly, our preliminary deep learning model predicted the LN stage in patients with colon cancer with a higher AUROC (0.860 vs 0.486) than the present study.[47] The discrepancy in diagnostic performance can be attributed to weak points of the preliminary study which included a smaller sample size (123 versus 1201 in the present study) and differences in deep learning architecture (DenseNet[258] versus ResNet-50 in the present study). Compared with a recent radiomics study, the model in this study achieved a worse diagnostic performance with lower AUROC (0.486 vs 0.825), specificity (6% vs 86%), and accuracy (42% vs 79%).[51] Importantly, the present study included only patients with colon cancer, however, our meta-analysis reported a higher diagnostic performance by radiomics models in comparison with the present study (AUROC 0.727 vs 0.486). Moreover, the significant difference in patient characteristics across cohorts may

have affected the model's performance, however reports suggest that datasets with diverse patient cohorts mitigate bias of AI models.[259,260] Taken together, these results suggest that a radiomics-based approach using CT images is potentially more effective in predicting LN staging when compared to deep learning.

In clinical practice, the advantages of using a deep learning model over routine preoperative radiological LN staging include saving the substantial cost of radiology reporting and potentially improved accuracy leading to better targeting of treatment options. In comparison with previous studies, the sensitivity of our deep learning model may be higher but the model achieved consistently lower AUCs, accuracy, and specificities.[237,252,261] This finding suggests that radiologists have a higher diagnostic capability in staging regional LNs on CT imaging in patients with colon cancer compared to the deep learning model in this study.

Several limitations of this study should be noted. First, segmentation of LNs was done manually, which inherently leads to interobserver and intraobserver variability. Variability in segmenting LNs might lead to inconsistency in the extracted imaging features and subsequently influence the classification of LNs. In the future, this could be addressed with the use of automated segmentation tools which are rather less time-consuming and remove interobserver variability. Second, CT images were collected from different scanners, resulting in wide heterogeneity in imaging hardware and acquisition protocols. Regardless, selecting a single imaging protocol is an unrealistic reflection of daily clinical practice and would have made the results non-generalizable. Third, the results of this study were from two institutions, so multicentre validation is required to assess reproducibility.

6.6 Conclusion

This study suggests a deep learning ResNet-50 model is not reliable in comparison with the current clinical standard in predicting LN status on preoperative staging CT in patients with colon cancer.

CHAPTER 7: ARTIFICIAL INTELLIGENCE FOR BODY COMPOSITION AND SARCOPENIA EVALUATION ON COMPUTED TOMOGRAPHY: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Statement of Authorship

Title of Paper	Artificial intelligence for body composition and sarcopenia evaluation on computed tomography: A systematic review and meta-analysis.
Publication Status	Published
Publication Details	Bedrikovetski S, Seow W, Kroon HM, Traeger L, Moore JW, Sammour T. Artificial intelligence for body composition and sarcopenia evaluation on computed tomography: A systematic review and meta-analysis. Eur J Radiol. 2022 Apr;149:110218. doi: 10.1016/j.ejrad.2022.110218. Epub 2022 Feb 15. PMID: 35183899.

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Name of Principal Author (Candidate)	Sergei Bedrikovetski		
Contribution to the Paper	Conception and design of the work Data acquisition Analysis and interpretation of data Drafting the final manuscript		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	01/08/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Warren Seow		
Contribution to the Paper	Conception and design of the work Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		
Signature		Date	01/08/2022
Name of Co-Author	Hidde M Kroon		
Contribution to the Paper	Conception and design of the work Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		

Signature		Date	01/08/2022
Name of Co-Author	Luke H Traeger		
Contribution to the Paper	Conception and design of the work Data acquisition Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		
Signature		Date	01/08/2022
Name of Co-Author	James W Moore		
Contribution to the Paper	Conception and design of the work Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		
Signature		Date	01/08/2022
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Contribution to the Paper	Conception and design of the work Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		
Signature		Date	01/08/2022

7.1 Abstract

Introduction: Tracing muscle groups manually on CT to calculate body composition parameters and diagnose sarcopenia is costly and time consuming. Artificial Intelligence (AI) provides an opportunity to automate this process. In this systematic review, we aimed to assess the performance of CT-based AI segmentation models used for body composition analysis.

Method: We systematically searched PubMed (MEDLINE), Embase, Web of Science and Scopus for studies published from January 1, 2011, to May 27, 2021. Studies using AI models for assessment of body composition and sarcopenia on CT scans were included. Excluded were studies that used muscle strength, physical performance data, DXA and MRI. Meta-analysis was conducted on the reported Dice Similarity Coefficient (DSC) and Jaccard Similarity Coefficient (JSC) of AI models.

Results: 284 studies were identified, of which 24 could be included in the systematic review. Among them, 15 were included in the meta-analysis, all of which used deep learning. Deep learning models for Skeletal Muscle (SM) segmentation performed with a pooled DSC of 0.941 (95%CI 0.923-0.959) and a pooled JSC of 0.967 (95%CI 0.949-0.986). Additionally, a pooled DSC of 0.967 (95%CI 0.958-0.978), 0.963 (95%CI 0.957-0.969) and 0.970 (95%CI 0.944-0.996) was observed for segmentation of Subcutaneous Adipose Tissue (SAT), Visceral Adipose Tissue (VAT), and bone, respectively. SM studies suffered from significant publication bias, and heterogeneity among the included studies was considerable.

Conclusions: CT-based deep learning models can facilitate the automated segmentation of body composition and aid in sarcopenia diagnosis. More rigorous guidelines and comparative studies are required to assess the efficacy of AI segmentation models before incorporating these into clinical practice.

7.2 Introduction

Progressive loss of muscle mass sets in at approximately 50 years of age and is the primary body composition change associated with aging.[105] Sarcopenia, characterised by the progressive and generalised loss of skeletal muscle mass and strength, is of particular clinical interest. Approximately 24% of adults aged 65-70 years old develop sarcopenia, largely attributed to reduced nutritional intake, physical inactivity and altered metabolic response.[262,263] Sarcopenic patients have a higher risk of complications, longer hospital stay and mortality after surgery.[264-266] Sarcopenia and changes in body composition have also been identified as risk factors for poor clinical outcomes in patients with cancer, such as chemotherapy toxicity and worse overall survival.[267-270]

Preoperative diagnosis of sarcopenia, by using body composition analysis, can therefore help clinicians to predict the patient's fitness and assist in better triaging and targeting of treatments, as well as in obtaining appropriate risk assessment for informed consent.[271] The standard approach to assess body composition is to measure the quantity and distribution of body fat and lean muscle mass.[114,272] While several imaging techniques are available to measure body composition, Computer Tomography (CT) is used most commonly due to accuracy and wide availability. Since CT is a routine part of staging for most cancers, relevant images are available for most patients at relevant time points.[273,274] However, despite the availability of CT, body composition parameters are not routinely calculated in clinical practice. This is, in part, due to the lack of readily available automated measuring tools, making body composition calculations burdensome, time consuming, and costly. In addition, manual segmentation analysis is limited by inter-observer variability, fat infiltration which results in overestimation of muscle mass, and practical considerations such as time restrictions that impact health service efficiencies.[109]

Artificial Intelligence (AI) has the potential to automate this labour-intensive task.[275] Radiomics is a subset of AI and consists of models based on large scale quantitative analyses of hand-designed image features. Radiomics is most commonly used for classification and segmentation tasks.[276] However, radiomics hand-designed features are based on traditional metrics and do not have self-learning possibility, limiting the future potential of these models. Deep learning models can overcome this by learning hierarchical features in a self-taught manner[277] and have shown promising results in skeletal muscle and body composition segmentation on CT scans from cancer patients.[278] In particular, deep Convolutional Neural Networks (CNNs) are able extract and select features jointly with classification within the optimization of the same architecture, hence allowing the performance to be calibrated in a systemic fashion.[279] In the era of precision medicine, AI segmentation models capable of evaluating body composition could be integrated into daily clinical practice by streamlining sarcopenia diagnosis and providing additional data to examinations performed for various clinical indications. With routine accurate measurement of body composition, clinicians may have the added information required to prevent or delay adverse outcomes with a more tailored treatment plan, ultimately improving the care of sarcopenic patients.[280] This review aims to assess the performance of CT-based AI segmentation models used for body composition analysis and sarcopenia diagnosis.

7.3 Materials and methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[281] The protocol was registered a priori with the international prospective register of systematic reviews (PROSPERO; CRD42021257540).

7.3.1 Search Strategy

We systematically searched PubMed (MEDLINE), Embase, Web of Science and Scopus for studies published between 1 January 2011 and 27 May 2021. The following search terms were used: artificial intelligence, deep learning, convolutional neural network, machine learning, automatic detection, vector machine, radiomics, radiomic, CT, age-related sarcopenia, body composition, dynapenia, myopenia, sarcopenic obesity, sarcopenia (Appendix D: Table 1). Reference lists of articles retrieved were searched manually to potentially identify additional eligible studies.

7.3.2 Selection of studies

Studies were included if they reported on the use of AI models to predict sarcopenia and/or estimate body composition from segmentation. The studies also included if they reported classification from CT scans at the level of C1-S5. Studies that used muscle strength, physical performance data, Dual-Energy X-ray Absorptiometry (DXA), Bioelectrical Impedance Analysis (BIA) or Magnetic Resonance imaging (MRI) modalities were excluded. Case reports, editorials, letters, reviews, comments, autopsy studies, book chapters and conference abstracts as well as studies that were not written in English were also excluded.

7.3.3 Data Extraction and quality assessment

Two investigators (SB and WS) with more than 2 years' experience in AI radiology research screened the studies on title, abstract and full text independently. Any disagreements were resolved by consensus or discussion with a third reviewer (TS) with over 10 years' experience in surgery and clinical research. Information was extracted by the same two investigators (SB and WS) included first author, year of publication, total number of patients, testing sample, population, gender, age, segmented region, tissues, AI model and segmentation performance metrics (Dice similarity coefficient and Jaccard index). The quality of the included studies was independently assessed by the two investigators (SB and WS) using the CLAIM checklist based on a previous review

(Appendix D: Table 2).[253,282] In case of uncertainty regarding a specific parameter a third reviewer (TS) was consulted to reach final consensus.

7.3.4 Statistical Analysis

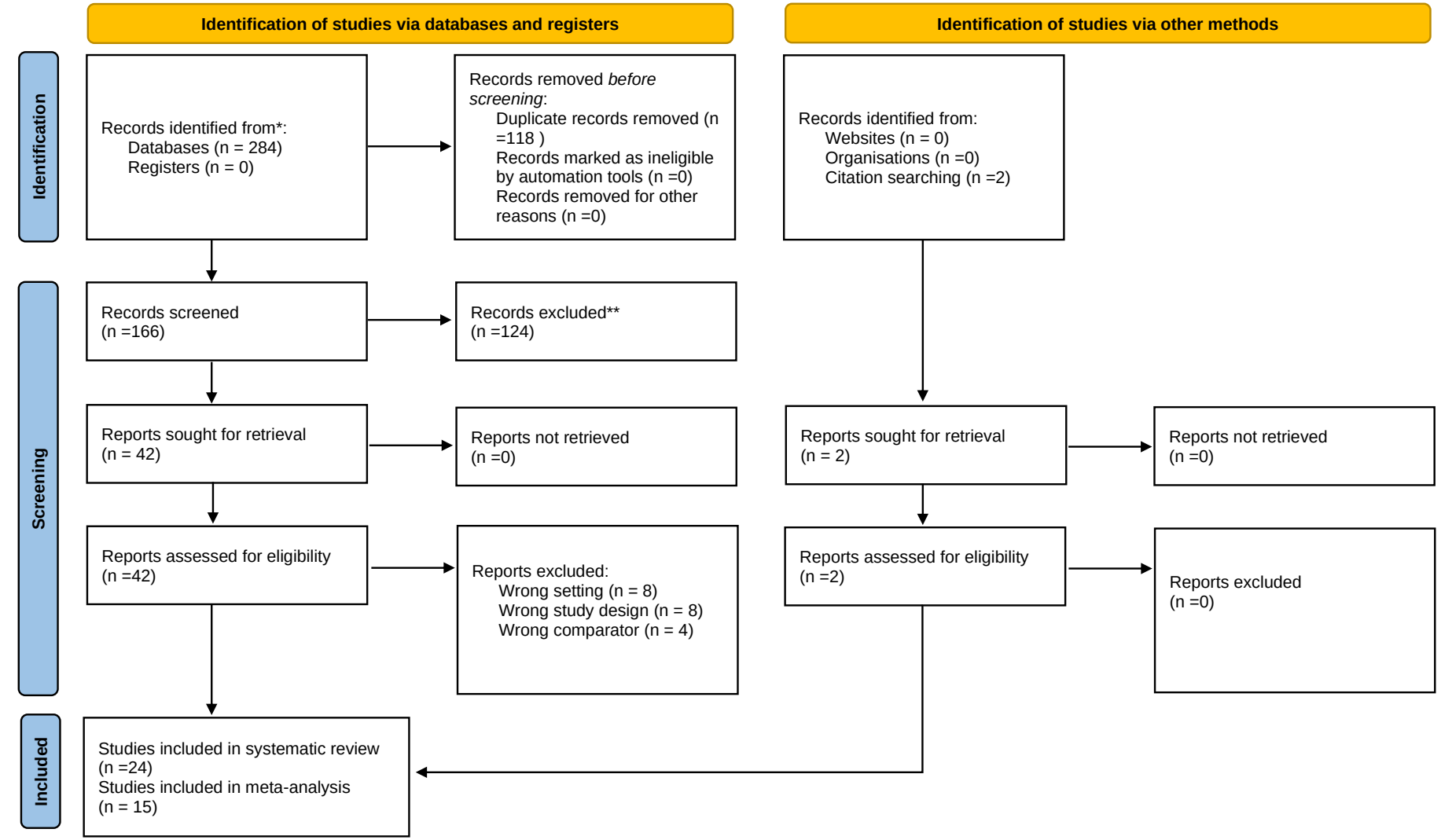
All statistical analyses were conducted using StatsDirect software (Version 3.3, Stats Direct Ltd., Altrincham, UK). To estimate the overall performance of AI segmentation models, a random-effects model meta-analysis was conducted, due to an observed high heterogeneity between included studies.[192] To be included in the meta-analysis, studies needed to have reported the mean Dice similarity coefficient (DSC) and/or the Jaccard similarity coefficient (JSC), in combination with a Standard Deviation (SD), Standard Error (SE) or 95% Confidence Interval (95%CI). In studies where 95%CI was not reported, the values were manually derived using total sample size, sample mean and SD.[283]

DSC and JSC are similarity measures used to quantify the accuracy of image segmentation methods. Both measures range from 0.0 (no overlap) to 1.0 (complete overlap) between automated and manual segmentations.[284] In this meta-analysis a good overlap was considered when the DSC or JSC >0.8 and a poor overlap when DSC or JSC <0.5. Using the summary meta-analysis function, pooled estimates of the DSC and JSC were obtained. Data were presented as weighted mean [95%CI]. The effect of heterogeneity was assessed through the Higgins I^2 metric. The Higgins I^2 test measures the degree of inconsistency between studies, where a value >75% indicates considerable heterogeneity and a value of <40% indicates low heterogeneity.[283] Publication bias was determined on both Egger's test and funnel plots.[285]

7.4 Results

7.4.1 Study Characteristics

A total of 24 studies were eligible for systematic review, from which 15 were eventually included for meta-analysis. The remaining 9 studies did not provide sufficient data (Figure. 20). Twenty-three studies (96%) were retrospective, and one study had a prospective design (4%). There were 13 (54%) single-centre and 11 (46%) multicentre studies. Nine studies (38%) comprised of oncological patients including lymphatic, head and neck, breast, lung, gastric, pancreatic, renal, ovarian and colorectal cancer. Four studies (17%) comprised of patients with benign conditions including COPD, risk of cardiac disease, liver cirrhosis, lumbar degeneration and four (17%) studies comprised of a mixture of oncologic and non-oncologic patients. The remining seven (29%) studies did not report their patient population. Of the studies that reported baseline characteristics, all were mixed gender studies with a predominant male population with an average age between 31 to 83 years. Twenty-two studies (92%) measured body composition within the region of the L3 vertebrae. Fifteen studies reported different combinations of body composition comprising of Skeletal Muscle (SM), Subcutaneous Adipose Tissue (SAT), Visceral Adipose Tissue (VAT) and bone. The remaining nine studies measured only one component of body composition. Twenty-three studies (96%) used a deep learning model, and one study used radiomics as method for automating segmentation (Table 15).



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Figure. 20 PRISMA flow chart of literature sear

Table 15 Study Characteristics

Author, year	Study design	Single/ Multi centre	Patients (testing cohort)	Population	Gender, Male/Female	Age, years	Region	Tissues	AI model
Kroll et al., 2021[286]	Retrospective	Single centre	966 (100)	Healthy individuals with increased cardiac risk	334/632	59.3± 9.6	T4-T9	SAT, SM	DL
Borrelli et al., 2021[287]	Retrospective	Multi centre	124 (74)	Lymphoma	32/18	61 (41-81)	L3	SAT, SM	DL
Amarasinghe et al., 2021[288]	Retrospective	Multi centre	66 (42)	NSCLC	42/24	66.94 ±9.81	L3	SM	DL
Ackermans et al., 2021[289]	Retrospective	Multi centre	3413 (233)	Colorectal cancer, Ovarian cancer, Pancreatic cancer, Polytrauma patients	156/77[a]	74 (10-88)[a]	L3	SAT, VAT, SM	DL
Magudia et al., 2021 [290]	Retrospective	Multi centre	604 (89)	Pancreatic cancer	5192/6936	52±17	L3	SAT, VAT, SM	DL
Zopfs et al., 2020 [291]	Retrospective	Multi centre	62	-	34/28	61.8± 15.7, 62.1± 15	T10 – S5	SAT, VAT	DL
Burns et al., 2020 [275]	Retrospective	Single centre	102 (51)	-	49/53	66.7± 5.8	L1 – 5	SM	DL
Koitka et al., 2020 [292]	Retrospective	Single centre	40 (10)	-	-	-	L3	SAT, SM, Bone	DL
Park et al., 2020[293]	Retrospective	Multi centre	946 (479)	Gastric cancer, Pancreatic cancer, Sepsis, Healthy individuals	571/375	56.1± 13.9, 56.6± 14.2, 61.1± 11.1	L3	SAT, VAT, SM	DL

Liu et al., 2020[294]	Retrospective	Single centre	38 (75)	Minimally abnormal, cancer	25/13	31-83	L3	SAT, VAT, SM	DL
Paris et al., 2020[295]	Retrospective	Multi centre	893 (89)	Renal and liver donors, Critically ill, Liver cirrhosis, Pancreatic cancer, Renal cell carcinoma	46/43[a]	53.9± 15.6[a]	L3	SAT, VAT, SM	DL
Hemke et al.,2020[296]	Retrospective	Single centre	200 (20)	-	102/98	49.9± 17.7	C1 – S4	SAT, SM, Bone	DL
Blanc-Durand et al., 2020[297]	Retrospective	Multi centre	1025 (500)	-	-	-	L3	SM	DL
Nowak et al., 2020[298]	Retrospective	Single centre	1143 (171)	Cardiac comorbidities, Liver cirrhosis	584/559	77±11	L3	SAT, VAT, SM, Bone	DL
Dong et al.,2019[299]	Retrospective	Single centre	99 (30)	NSCLC	63/36	52.7± 12.3	L3	SM	Radiomics
Graffy et al.,2019[300]	Retrospective	Single centre	8037 (9310)	-	3555/4482	57.1± 7.8	L3	SM	DL
Barnard et al.,2019[301]	Retrospective	Multi centre	2084 (209)	Lung cancer	1336/748	70-74	L3	SM	DL
Hashimoto et al.,2019[302]	Prospective	Single centre	100	Healthy individuals, Degenerative lumbar disease	36/64	51±5.8, 53.5±7	L4	VAT	DL
Dabiri et al.,2019[278]	Retrospective	Multi centre	3774 (1327)	Colorectal cancer,	-	-	L3	SAT, VAT, SM	DL

				Breast cancer, Head, neck, and lung cancer					
Weston et al., 2019[303]	Retrospective	Single centre	1429 (270)	Pancreatic cancer, Renal cell cancer, Transitional cell carcinoma, GI cancer, Liver cancer	878/551	66.5± 11	L3	SAT, VAT, SM, Bone	DL
Liu et al., 2019[304]	Retrospective	Single centre	216 (115)	-	-	-	L3	SM	DL
Gonzalez et al. 2018[305]	Retrospective	Multi centre	3000 (1000)	COPD	-	-	T4	SAT, SM	DL
Wang et al., 2017[306]	Retrospective	Single centre	40 (20)	Ovarian cancer	-	-	L3	SAT, VAT	DL
Lee et al., 2017[307]	Retrospective	Single centre	400 (150)	Lung cancer	200/200	63±12	L3	SM	DL

NSCLC, non-small cell lung cancer, COPD, chronic obstructive pulmonary disease DL, deep learning; SM, Skeletal muscle, SAT, Subcutaneous adipose tissue; VAT, Visceral adipose tissue

[a] Data extracted from testing sample.

7.4.2 Pooled performance using the DSC

Fourteen studies assessed the performance of SM segmentation in deep learning models (Table 16).[278,288,290,293-295,297,298,300,301,303-305,307] Meta-analysis showed a pooled weighted mean DSC of 0.941% (95%CI: 0.927-0.947). Eight studies assessed the performance of SAT segmentation in deep learning models.[290,293-295,298,303,305,306] Meta-analysis pooled analysis showed a weighted mean DSC of 0.967 (95%CI: 0.958-0.978). Seven studies assessed performance of VAT segmentation deep learning models.[290,293-295,298,303,306] The meta-analysis pooled weighted mean DSC was 0.963 (95%CI: 0.957-0.969). Three studies suitable for meta-analysis assessed the performance of bone segmentation deep learning models.[294,298,303] The weighted mean DSC was found to be 0.970 (95%CI: 0.944-0.996) (Table 17, Figure. 21).

Table 16 DSC and JSC of AI segmentation models								
Author, year	**DSC**							
	SM (mean ±SD)	**95%CI**	**SAT (mean ±SD)**	**95%CI**	**VAT (mean ±SD)**	**95%CI**	**Bone (mean ±SD)**	**95%CI**
Kroll et al., 2021[286]	0.960	-	0.970	-	-	-	-	-
Borrelli et al., 2021[287]	0.940	-	0.960	-	-	-	-	-
Amarasinghe et al., 2021[288]	0.92 ± 0.06	0.902 to 0.938	-	-	-	-	-	-
Ackermans et al., 2021[289]	-	-	-	-	-	-	-	-
Magudia et al. 2021[290]	0.97 ± 0.03	0.964 to 0.976	0.98 ± 0.02	0.976 to 0.984	0.95 ± 0.10	0.929 to 0.971	-	-
Zopfs et al. 2020[291]	0.95	-	-	-	-	-	-	-
Burns et al. 2020[275]	0.940	-	-	-	-	-	-	-
Koitka et al. 2020[292]	0.9334	-	0.9623	-	0.973	-	0.9423	-
Park et al. 2020[293]	0.96 ± 0.02	0.958 to 0.962	0.97 ± 0.03	0.968 to 0.972	0.97 ± 0.01	0.969 to 0.971	-	-
Liu et al. 2020[294]	0.928 ± 0.038	0.919 to 0.937	0.975 ± 0.020	0.970 to 0.980	0.943 ± 0.032	0.936 to 0.950	0.968 ± 0.024	0.963 to 0.973
Paris et al. 2020[295]	0.983 ± 0.013	0.98 to 0.986	0.986 ± 0.016	0.983 to 0.989	0.979 ± 0.019	0.975 to 0.983	-	-
Hemke et al. 2020[296]	0.96	-	0.97	-	-	-	0.93	-
Blanc-Durand et al. 2020[297]	0.93 ± 0.03	0.927 to 0.933	-	-	-	-	-	-
Nowak et al. 2020[298]	0.948 ± 0.022	0.945 to 0.951	0.979 ± 0.014	0.977 to 0.981	0.962 ± 0.037	0.956 to 0.968	0.992 ± 0.005	0.991 to 0.993
Dong et al. 2019[299]	0.870	-	-	-	-	-	-	-
Graffy et al. 2019[300]	0.938 ± 0.028	0.937 to 0.939	-	-	-	-	-	-
Barnard et al. 2019[301]	0.94 ± 0.04	0.935 to 0.945	-	-	-	-	-	-
Dabiri et al.,2019 [278]	0.9912 ±0.01	0.991 to 0.992	-	-	-	-	-	-
Weston et al. 2019[303]	0.88 ± 0.07	0.872 to 0.888	0.93 ± 0.06	0.923 to 0.937	0.97 ± 0.02	0.968 to 0.972	0.95 ± 0.05	0.944 to 0.956
Liu et al. 2019[304]	0.9172 ± 0.1325	0.893 to 0.941	-	-	-	-	-	-

Gonzalez et al. 2018[305]	0.928 ± 0.051[a]	0.925 to 0.931	0.942 ± 0.070[b]	0.938 to 0.946	-	-	-	-
Wang et al. 2017[306]	-	-	0.9797 ± 0.0145	0.973 to 0.986	0.9150 ± 0.0624	0.888 to 0.942	-	-
Lee et al. 2017[307]	0.93 ± 0.02	0.927 to 0.933	-	-	-	-	-	-
	JSC							
Dabiri et al.,2019[278]	0.9827 ±0.0188	0.982 to 0.984	-	-	-	-	-	-
Weston et al. 2019[303]	0.92 ± 0.04	0.915 to 0.925	0.96 ± 0.04	0.955 to 0.965	0.90 ± 0.13	0.885 to 0.915	0.97 ± 0.03	0.966 to 0.974
Liu et al. 2019[304]	0.9986 ± 0.0029	0.998 to 0.999	-	-	-	-	-	-

DSC, Dice similarity coefficient; JSC, Jaccard similarity coefficient; SM, Skeletal muscle; SAT, Subcutaneous adipose tissue; VAT, Visceral adipose tissue;

[a] Data extracted from right pectoralis muscle.

[b] Data extracted from left subcutaneous fat.

Table 17 Pooled DSC and JSC of segmentation DL models							
	References of studies meta-analysed	**Pooled estimate, weighted mean**	**95%CI**	**I^2, %**	**Egger's bias**	**Egger's 95%CI**	**Egger's P-value**
DSC							
SM	278,288,290,293-295,297,298,300,301,303-305,307	0.941	0.923 to 0.959	99.9	-23.34	-44.16 to -2.52	0.031
SAT	290,293-295,298,303,305,306	0.967	0.958 to 0.978	99.0	-7.15	-24.9 to 10.6	0.363
VAT	290,293-295,298,303,306	0.963	0.957 to 0.969	94.0	-2.92	-8.03 to 2.18	0.201
Bone	294,298,303	0.970	0.944 to 0.996	99.0	N/A[a]	N/A[a]	N/A[a]
JSC							
SM	278,303,304	0.967	0.949 to 0.986	99.9	N/A[a]	N/A[a]	N/A[a]

DSC, Dice similarity coefficient; JSC, Jaccard similarity coefficient

[a] Egger could not be calculated given the low number of studies.

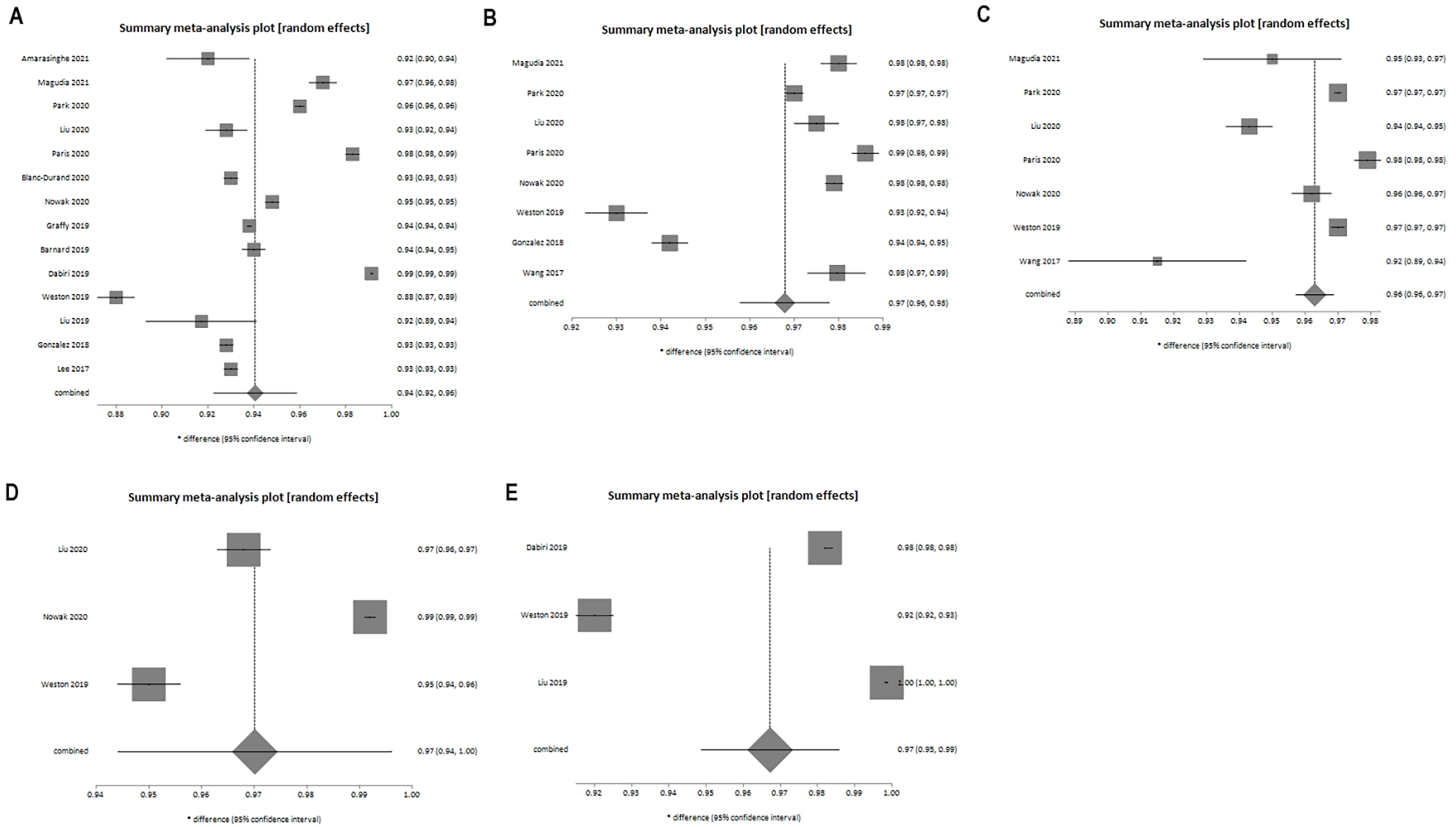


Figure. 21 Forest plots of included studies that assessed the performance of body composition segmentation using deep learning models. Legend: DSC, dice similarity coefficient; JSC, Jaccard similarity coefficient. (A) DSC of skeletal muscle, (B) DSC of subcutaneous adipose tissue, (C) DSC of visceral adipose tissue, (D) DSC of bone and (E) JSC of skeletal muscle.

7.4.3 Performance using the JSC

Three studies provided sufficient information to evaluate the SM segmentation performance of deep learning models using JSC (Figure. 21).[278,303,304] Overall, the JSC was found to be 0.967 (95%CI: 0.949-0.986).

7.4.4 Publication bias

Funnel plots for SM, SAT and VAT deep learning segmentation studies assessed in the meta-analysis are shown in Figure. 22. Egger's regression test on SM funnel plot showed a significant publication bias (SM intercept= -23.34 (95%CI: -44.16 to -2.52), P=0.031). SAT and VAT funnel plots yielded similar outcomes, although did not show a publication bias (SAT intercept= 0.363 (95%CI: -24.9, 10.6), P=0.363; VAT intercept =-2.92 (95%CI: -8.03, 2.18), P=0.201) (Table 3). Egger's bias in DSC bone and JSC SM could not be calculated due to low number of studies.

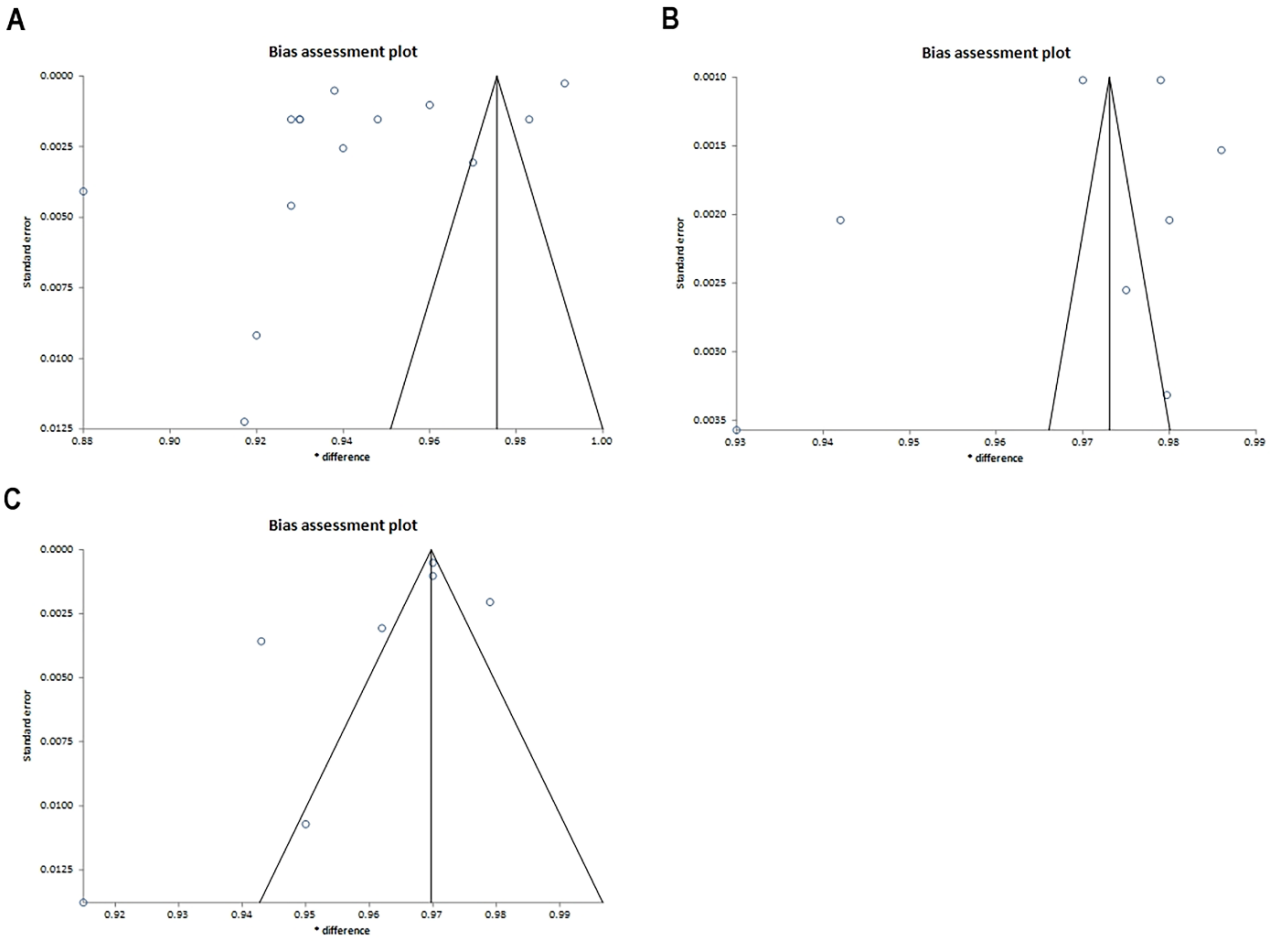


Figure. 22 Funnel plots for meta-analysis of (A) skeletal muscle, (B) subcutaneous adipose tissue and (C) visceral adipose tissue.

7.4.5 CLAIM adherence

The CLAIM items of the 24 studies expressed as a percentage of the idea score according to the six key sections are shown in Figure. 23. In the Title/Abstract section, 83.3% of studies clarified the AI methodology in the title and performed a well-structured abstract. The remaining 16.7%, the AI method was unclear in the title, or the journal did not require a structured abstract. In the Introduction section, almost all studies (98%) clearly addressed the scientific and clinical background, howbeit 2% of studies had insufficient information on the clinical role of the AI approach. In the Methods section, 69.6% of studies described the study's methodology in a thorough and clear manner, enabling reader to reproduce the experiments described and 26.4% of studies failed to report specific items in the methodology. A few items such as selection of data subsets, how missing data were handled and ensembling techniques were not applicable in 4% of studies. In the Results section, 55.8% of studies presented the results in sufficient detail, conversely 44.2% of studies missed the demographic and clinical characteristics, 95% confidence intervals when displaying DSC/JCC and failure analysis of incorrectly classified cases was rare. In the Discussion section, 95.8% of studies discussed limitations and the implications of segmentation models in the clinical setting.

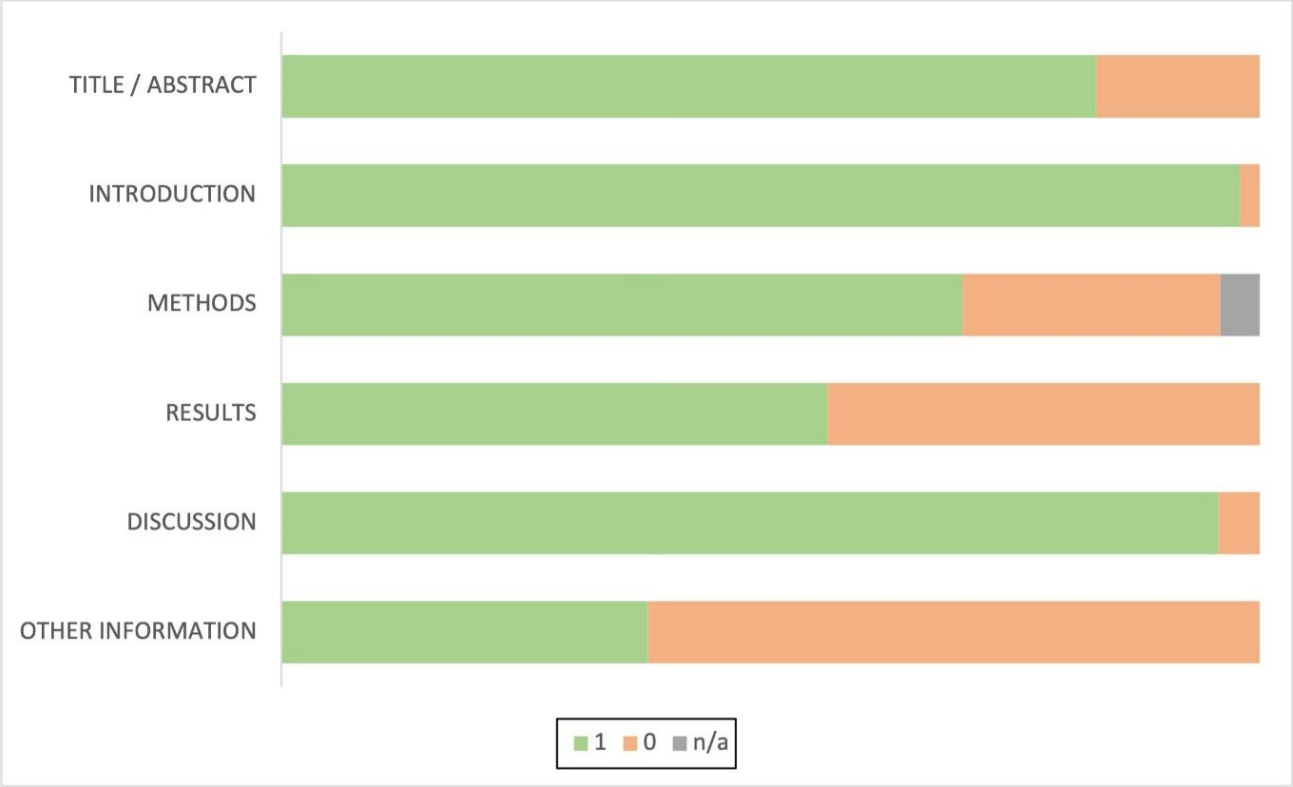


Figure. 23 CLAIM items of the 24 included studies expressed as percentage of the ideal score according to the six key domains. CLAIM, Checklist for Artificial Intelligence in Medical Imaging

7.5 Discussion

This systematic review and meta-analysis summarizes the existing evidence on the performance of CT-based AI models for body composition and sarcopenia assessment. The principal finding was that despite substantial heterogeneity among the included studies, deep learning models had a good DSC and JSC for SM segmentation and a good DSC for SAT, VAT and bone segmentation.

The criteria used to define sarcopenia is varied and may depend on measurement level, anatomy measured, software used and targeted population.[308,309] In early 2018, the European working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia by low levels of measures for three parameters, (1) muscle strength, (2) muscle quality/quantity and (3) physical performance as an indicator of severity.[310] Sarcopenia is of significant clinical importance, as the loss of skeletal muscle mass and strength leads to worse outcomes for patients with either malignant or benign disease. Diagnosis of sarcopenia requires CT imaging to account for total skeletal muscle cross-sectional area at standardised lumbar vertebrae levels.[274,311] Also at this level, adipose tissue and bone compartments can be assessed simultaneously. However, robust measures of body composition are difficult to obtain routinely in clinical practice due to cost, time and the training required.[312] Our findings show that with current advances, AI models are able to perform automated body composition analysis using CT imaging quite effectively. Thus, detecting sarcopenia using CT-based AI models might prove valuable in identifying patients with such conditions not only when undergoing CT for the purpose of sarcopenia detection, but virtually on any CT scan regardless of the clinical indication. Moreover, incidental findings are frequently seen on routine CT examinations in sarcopenic patients and while most unexpected anomalies are unlikely to be clinically relevant, occasionally such a finding can be beneficial and even lifesaving.[313-315]

This review does also highlight several methodological weaknesses within current literature describing the use of AI for body composition analysis. Most studies (96%) were retrospective in

design with an inherent risk of selection bias. A further 54% of studies were single-centred and limited by a small sample size and lack of adequate external validity. The use of different CT acquisition protocols (intravenous contrast, field of view, slice thickness, image quality, radiation dose protocols and scanner manufacturer) and geographically and ethnically diverse patient populations may have attributed to the heterogeneity observed. The combination of the use of varying imaging protocols in diverse patient populations may display different body composition phenotypes and muscle density, potentially leading to biases during training in some of the included studies, which may degrade overall segmentation accuracy. On the other hand, a small number of studies reported a patient population that skewed towards older and overweight patients often with substantial pathology. In these instances, a larger and more diverse sample would be required to create a more generalizable AI model.[301]

The deep learning approach used in all studies included in the meta-analysis appeared to achieve high accuracy by using large manually segmented CT datasets fed into neural networks to learn image features and performs well segmenting lean muscle and adipose tissue.[316] However, the high variability in sample size among included studies can lead to overfitting because certain subgroups may not be represented in small sample sizes, or underfitting given the low variance and high bias in large sample sizes. Most studies predominantly relied on manual extraction of each CT slice at a specific abdominal region in order to train the neural network architecture.[295,298,301] However, recent studies using CNN based models have shown promising results with automatically selecting CT slices at L3 vertebral level.[275,286,290,292,295,300,306,317-319] This could enable a more streamlined approach for muscle segmentation on CT imaging. Furthermore, to better assess muscle depletion, future studies may benefit from using multiple CT slices from different anatomical areas, to provide more detail on skeletal muscle mass.[290,296]

Current methods of AI body composition analysis, including sarcopenia and visceral adiposity, provide a binary result of whether the patient has the condition or not. This largely ignores baseline characteristics and complex parameters (e.g., grip strength and gate speed) that provide additional practical details for the diagnosis and severity of the condition. Also, AI segmentation models included in this review were tested on the assumption that the segmented slices were not affected by motion artefact, imperfect vertebral bodies, arms/hands in the field of view and/or surgical metal artefacts. All these factors, commonly encountered in patients, are known to negatively affect segmentation quality.[298] Further refinements to the deep learning segmentation model will therefore be required to account for these artefacts.

Lastly, several AI segmentation models can overestimate SM or VAT. Overlapping adjacent internal organs with SM due to similar CT Hounsfield units, can lead to a degree of misclassification.[275,288,289,291] Similarly, every voxel (volume element of the patient's tissue) with HU matching fat intensity is incorrectly counted as VAT, and should be excluded. This inability to distinguish VAT from fat within organs, reduces the accuracy of AI models.[292] This suggests that current deep learning models have not been trained with CT images that fully represent the variability of SM or VAT areas.

This review itself also has some limitations. Firstly, the pooled DSC and JSC of deep learning segmentation models should be interpreted with caution, as significant heterogeneity between the studies could have skewed the results. Secondly, body composition measures were extracted from different anatomical regions, thus the models would have extracted different semantic information within these regions, which may have affected the model's performance across the studies. Thirdly, the present review focused on CT-based AI segmentation models only, while dual-energy X-ray absorptiometry, ultrasound and magnetic resonance imaging were not investigated. Lastly, although

we used the CLAIM checklist to score studies, this is not yet classed as a validated assessment tool to determine quality of studies.

7.6 Conclusions

CT-based deep learning models can facilitate the automated segmentation of body composition and aid in sarcopenia diagnosis. More rigorous guidelines and comparative studies are required to assess the efficacy of AI segmentation models before incorporating these into clinical practice.

PART 2: PREDICTION OF LOCAL RESPONSE TO CHEMORADIATION IN LOCALLY ADVANCED RECTAL CANCER

CHAPTER 8: DOES SARCOPENIA PREDICT LOCAL RESPONSE RATES AFTER CHEMORADIOTHERAPY FOR LOCALLY ADVANCED RECTAL CANCER?

Statement of Authorship

Title of Paper	Does sarcopenia predict local response rates after chemoradiotherapy for locally advanced rectal cancer?
Publication Status	Accepted for Publication
Publication Details	Bedrikovetski S, Traeger L, Vather R, Sammour T, Moore JW. Does sarcopenia predict local response rates after chemoradiotherapy for locally advanced rectal cancer?. Dis Colon Rectum. (Forthcoming) 10.1097/DCR.0000000000002451

Principal Author

Name of Principal Author (Candidate)	Sergei Bedrikovetski		
Contribution to the Paper	Conception and design of the work Data acquisition Analysis and interpretation of data Drafting the final manuscript		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	01/08/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Luke H Traeger		
Contribution to the Paper	Conception and design of the work Data acquisition Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		
Signature		Date	01/08/2022
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Contribution to the Paper	Conception and design of the work Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		

Signature		Date	01/08/2022
Name of Co-Author	Tarik Sammour		
Contribution to the Paper	Conception and design of the work Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		
Signature		Date	01/08/2022
Name of Co-Author	James W Moore		
Contribution to the Paper	Conception and design of the work Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		
Signature		Date	01/08/2022

8.1 Abstract

Background: The predictive value of sarcopenia for tumour response to neoadjuvant chemoradiotherapy is unclear.

Objective: This study investigates the association between sarcopenia and pathological tumour regression grade after neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer.

Design: Retrospective cohort study from a prospectively collected database. Univariate logistic regression was performed to assess the association between sarcopenia and tumour response.

Settings: This study was conducted at two tertiary care centres.

Patients: Patients undergoing neoadjuvant chemoradiotherapy for locally advanced rectal cancer (T3/4, N0/+) between 2007-2018.

Intervention(s): Sarcopenia was diagnosed using gender-specific cut-offs of lean muscle mass. Using the initial staging computed tomography, lean muscle mass was estimated using the cross-sectional area of the psoas muscle at the level of the third lumbar vertebra, normalized for patient height.

Main Outcome Measures: The primary endpoint was pathological tumour regression grade, defined as good (Tumour regression grade 0/1) vs poor (Tumour regression grade 2/3).

Results: The study included 167 locally advanced rectal cancer patients with a median age of 60 years (20-91), 132 in the non-sarcopenia group and 35 in the sarcopenia group. Eighty nine percent were stage III. Six patients (5.4%) had a sustained complete clinical response, one patient did not respond to treatment and opted for non-operative management, the remaining 157 (94.0%) proceeded to surgery. Pathological data revealed no significant difference between good tumour regression grade patients in the sarcopenia group compared with the non-sarcopenia group. Univariate analysis revealed BMI$\geq$ 25 kg/m^2 to be risk factors for good tumour regression grade (P=0.002).

Limitations: This study was limited by its retrospective design and small sample size.

Conclusion: Sarcopenia is not a predictor of poor neoadjuvant chemoradiotherapy response in locally advanced rectal cancer patients. Increasing BMI was associated with good tumour regression grade. Future multicentred studies are warranted to validate this finding.

8.2 Introduction

The current standard of care for patients with Locally Advanced Rectal Cancer (LARC) consists of a multimodal approach with neoadjuvant Chemoradiotherapy (nCRT) followed by Total Mesorectal Excision (TME) and adjuvant chemotherapy.[320] This approach results in approximately 10 – 15% of patients achieving a pathological Complete Response (pCR) and offers most patients improved loco-regional control.[35,321] As a result, a significant shift in focus has been placed towards predicting tumour response given the higher rate of 5-year disease-free survival and overall survival for these patients.[322] A recent meta-analysis has shown patients with pCR are more likely to be older, have smaller and lower tumours, no clinical lymph node involvement and a wait time of more than 8 weeks prior to TME.[323] Hence, this subset of patients may potentially avoid a morbid operation by adopting a 'watch and wait' treatment strategy, which has demonstrated similar survival results but better functional outcomes.[324,325]

Despite its benefits nCRT, like many cancer therapies, often leads to adverse side effects such as loss of appetite, fatigue, vomiting and pain. This can cause significant weight loss and muscle degradation.[326] This reduction of lean muscle mass is termed sarcopenia, and is also associated with aging and advanced disease.[107] In 35% of gastrointestinal cancers, patients have cancer cachexia, a syndrome that includes sarcopenia alongside low Body Mass Index (BMI).[327,328] Recently, sarcopenia has been demonstrated to predict poorer immediate post-operative and long term outcomes following colorectal cancer and other malignancy related surgery.[116,329,330] Sarcopenia is also associated with increased toxicity and poor response rates to chemotherapy.[331] Computed Tomography (CT) is routinely performed during the preoperative staging of cancer. To quantify lean muscle mass, the cross sectional area of the psoas on a single CT slice mid-lumbar vertebrae serves as convenient tool.[114,332] Until now, only a single small study has examined the role of sarcopenia as a predictive factor for response to neoadjuvant chemoradiotherapy in LARC.[333] More

studies are required to understand the relationship of sarcopenia with treatment response. This study aimed to assess the role of sarcopenia as a predictor of response to nCRT in LARC patients.

8.3 Material and Methods

This retrospective study is reported according to the STROBE (Strengthening The Reporting Observational studies in Epidemiology) statement[334] and was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (HREC/19/CALHN/73) and the St. Andrews Hospital Ethics Committee (#116). A waiver of consent for low-risk studies was obtained.

8.3.1 Patients

Patients diagnosed with LARC, treated with nCRT between 2007 and 2018 were retrospectively identified from the Royal Adelaide Hospital and St. Andrews Hospital prospectively collected colorectal cancer database. The decision to offer nCRT was made following appropriate Multidisciplinary Team (MDT) discussion. All patients included in this study were treated according to the protocol with nCRT and no patient received Total Neoadjuvant Therapy (TNT). Patients were excluded if tumour height was not recorded, or if they had not undergone staging CT accessible by our local Picture Archiving and Communication System (PACS) or InteleViewer™ Australia. The nCRT protocol during the study period consisted of 50.4Gy/25 fractions over 5 weeks, with an option for dose escalation to 54Gy/27 fractions. Patients concurrently received either continuous infusional 5-fluorouracil (5-FU) or capecitabine orally 5 days per week. Surgery was scheduled 8-10 weeks after the radiotherapy for patients who did not achieve a clinical Complete Response (cCR) as assessed at flexible sigmoidoscopy +/- MRI at 8 weeks post completion of nCRT.

Medical records were reviewed to collect demographic information, clinical and pathological outcomes and postoperative complications. Specific characteristics included age, gender, height,

weight, BMI, body composition, post-treatment sarcopenia, American Society of Anaesthesiologists (ASA) score, tumour location, clinical stage and cCR. Operative findings included operation type, surgical approach, postoperative outcomes, return to theatre, 30-day readmission and 30-day mortality. Pathological stage was established based on the 8th edition of the American Joint Committee on Cancer (AJCC)[81] Colon and Rectal staging manual. Tumour Regression Grade (TRG on pathological assessment) was classified based on the AJCC/Modified Ryan Scheme.[335]

8.3.2 Sarcopenia assessment

To diagnose pre-treatment sarcopenia, lean muscle mass was measured on the pre-treatment staging CT scans based on the protocol defined by Jones et al. (2014).[114] In the diagnosis of post-treatment sarcopenia, lean muscle mass was calculated using restaging CT scans. An investigator was trained by a consultant surgeon to identify the psoas muscle at the third lumbar vertebrae on CT. Using the PACS or InteleViewer measuring ruler the cross-sectional of the psoas muscle at this level was measured. Total Psoas Area (TPA) was calculated by multiplying the longest anterior to posterior and transverse muscle diameters (Figure. 24). TPA was normalized for the patient's height squared (TPAmm^2/m^2) to calculate Total Psoas Area Index (TPAI). Sarcopenia was defined by using previously validated gender-specific cut-off points: <385 mm^2/m^2 in females and <545 mm^2/m^2 in males.[328] Patients were further classified based on level of severity. Cut-offs for severe sarcopenia were <300mm^2/m^2 for females and <420mm^2/m^2 for males. Mild sarcopenia cut-off values were between 300≤TPAI<385 mm^2/m^2 for females and 420≤TPAI<545 mm^2/m^2 for males.[336]

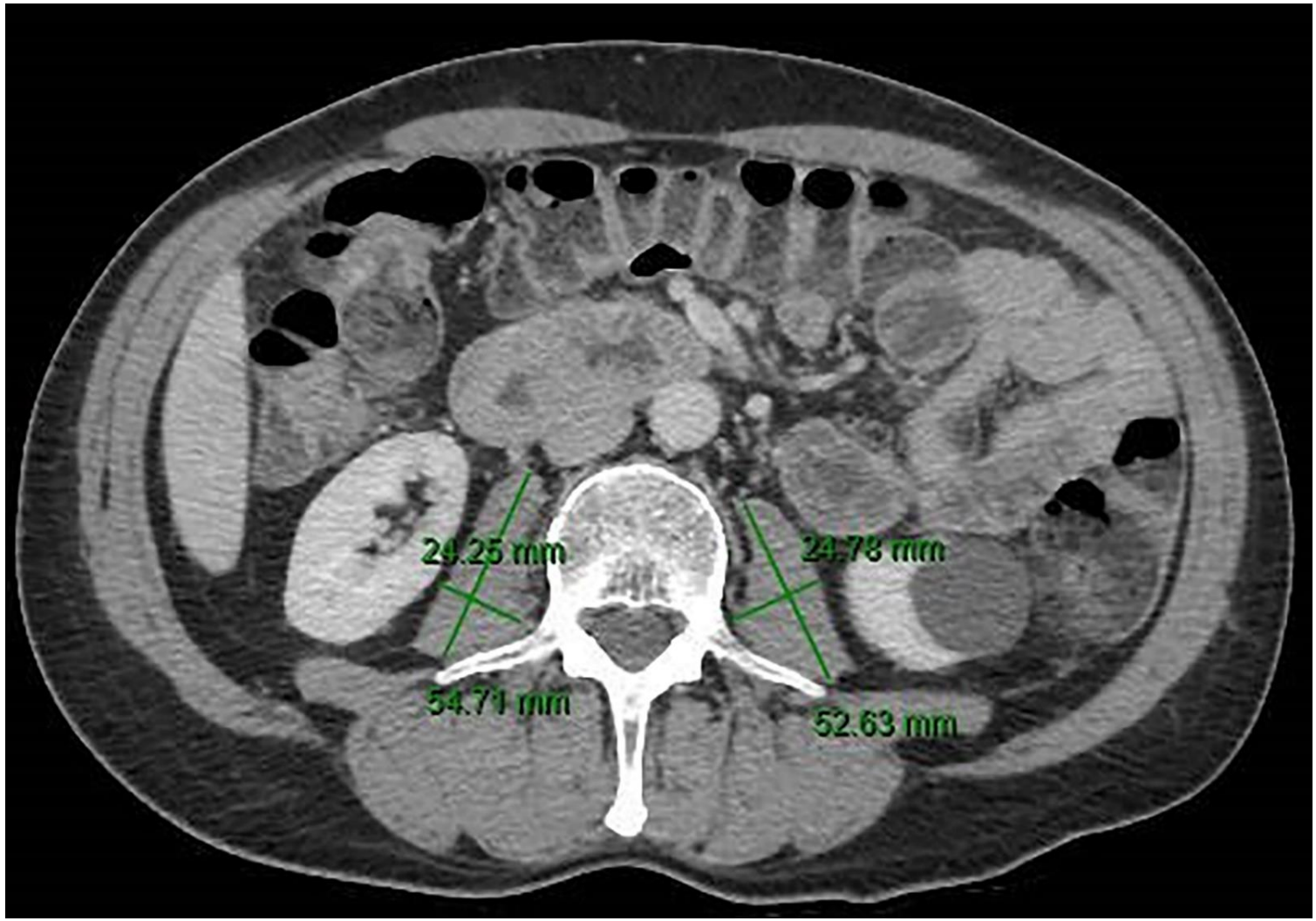

Figure. 24 Assessment of total psoas area index (TPAI). TPAI was assessed by measuring the longest anterior to posterior and transverse diameter (green lines) of the right and left psoas muscle on an axial computed tomography (CT) slice at the level of the 3rd lumbar vertebrae and normalized for the patients' height squared.

8.3.3 Endpoints

The primary endpoint was TRG on pathology, defined as good (TRG 0/1) or poor (TRG 2/3).[337] Secondary endpoints included pathological Complete Response (pCR) and assumed Complete Response (CR), based on surgical resection specimen assessment or, in cases achieving cCR, the absence of local regrowth at 2 years follow-up (assumed CR).

8.3.4 Statistical analysis

Parametricity was determined using the Shapiro-Wilk test. Normally distributed data was expressed as mean ± standard deviation and nonparametric data as median (range). Categorical data was expressed as numbers and percentages. Continuous data was compared using a student's t test or the Mann-Whitney U-test depending on the type of distribution. Univariate logistic regression analysis included binary variables age (<61 or ≥ 61 years), BMI (<25 or ≥25kg/m^2), presence of sarcopenia (yes or no) and sarcopenia severity (normal, mild sarcopenia, severe sarcopenia) as potential predictors of TRG. Categorical data was compared using chi-square test or Fisher's exact test. A P-value <0.05 was considered statistically significant. All statistical analysis was performed with SPSS 28.0 (IBM Corporation, Armonk, NY, USA).

8.4 Results

A total of 714 patients had a diagnosis of rectal cancer between 2007 and 2018, from which 167 LARC patients who underwent nCRT were eligible for inclusion in this study. A total of 384 patients were excluded for not receiving neoadjuvant treatment, 98 had short course radiotherapy, 20 were palliative due to metastasis, six were referred to another hospital, one declined surgery and 38 for not having height recorded or a preoperative CT scan to analyse (Figure. 25). The median age was 60 years (20-91) and 66.5% were male. There were 35 (21.0%) sarcopenic patients and 132 (79.0%) were non-sarcopenic. The median BMI was significantly higher in the non-sarcopenic group (NSG) than in the sarcopenic group (SG) (27.38 vs. 24.54 kg/m^2, P<0.003). The mean TPA

and mean TPAI were both significantly higher in the NSG compared to the SG (1947.50 vs. 1163.42mm^2, P<0.001; 647.73 vs. 379.02mm^2/m^2, P<0.001; respectively). Tumours were predominantly low rectal tumours (64.7%), 74.3% were cT3 and 89.8% were clinically node positive (cN+). Of the 167 LARC patients, one did not achieve a cCR and declined surgery, nine (5.4%) had cCR (and entered a watch and wait program) of which three local recurrences at 2 years were seen in the SG. Overall, six patients achieved a sustained cCR and 157 (94.0%) patients had surgical resection. Demographics and clinical findings are summarized in Table 18.

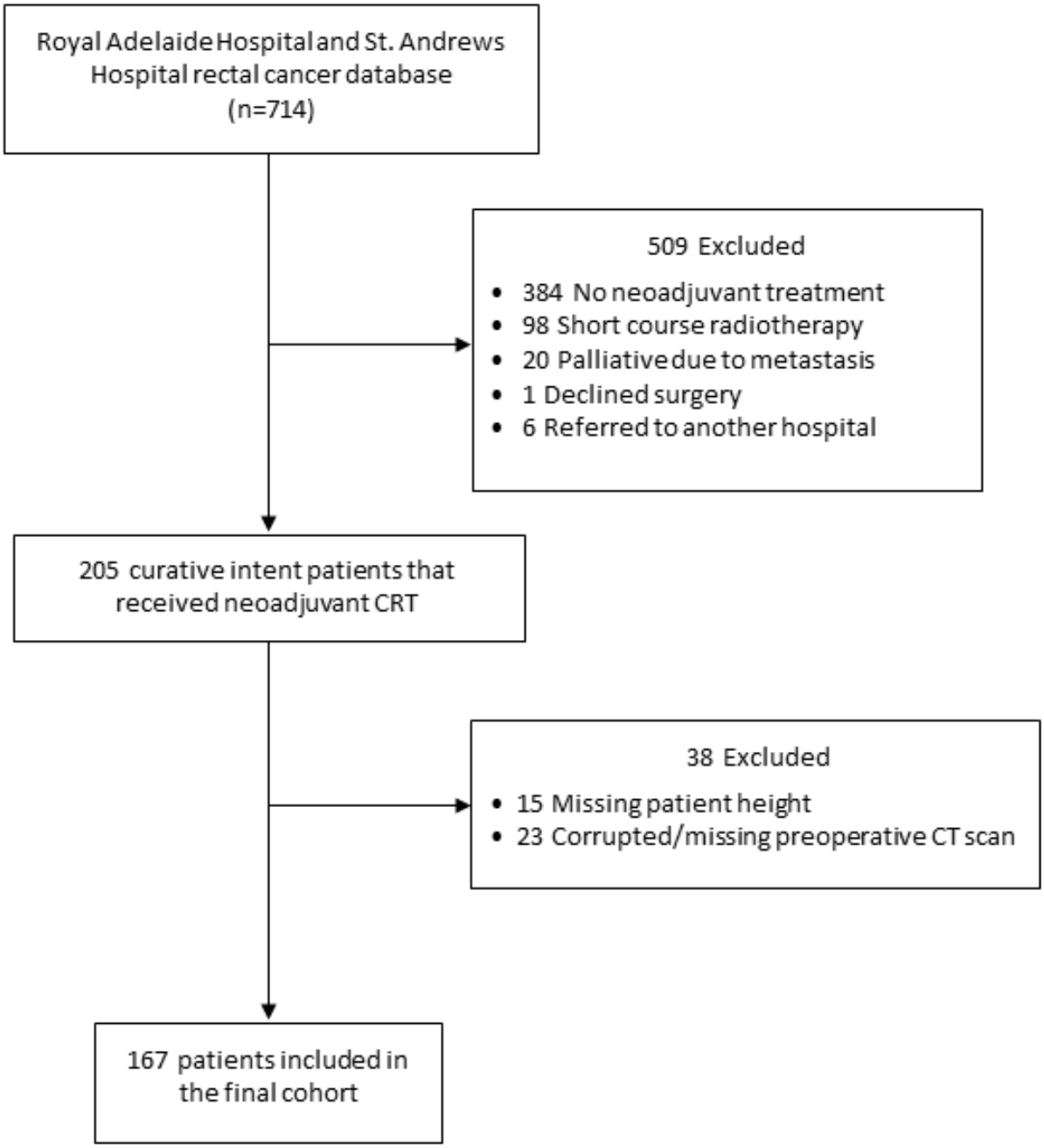

Figure. 25 Patient selection flowchart.

Table 18 Demographics and clinical findings				
Variables	**Total (n=167)**	**Sarcopenic (n=35)**	**Non-sarcopenic (n=132)**	**P value**
Age (years)	60 (20-91)	60 (20-91)	60 (23-84)	0.33
Gender				0.19
Male	111 (66.5)	20 (57.1)	91 (68.9)	
Female	56 (33.5)	15 (42.9)	41 (31.1)	
BMI (kg/m^2)	26.87 (12.57-56.64)	24.54 (12.57-34.20)	27.38 (15.42-56.64)	0.003
Body composition				
TPA (mm^2)	1778.00 (616.88-3979.07)	1163.42 (616.88-1703.00)	1947.50 (930.00-3979.070	<0.001
TPAI (mm^2/m^2)	605.15 (240.97-1393.18)	379.02 (240.97-540.40)	647.73 (387.61-1393.18)	<0.001
Post-treatment sarcopenia				N/A
Yes	N/A	N/A	5 (3.8)	
No	N/A	N/A	42 (31.8)	
Missing	N/A	N/A	85 (64.4)	
ASA				0.52
1-2	91 (56.9)	21 (61.8)	70 (55.6)	
3-4	69 (43.1)	13 (38.2)	56 (44.4)	
Tumour location				0.95
Upper (>12 cm)	10 (6.0)	2 (5.7)	8 (6.1)	
Mid (8-12 cm)	49 (29.3)	11 (31.4)	38 (28.8)	
Low (<8 cm)	108 (64.7)	22 (62.9)	86 (65.2)	
Clinical T stage				1.00
cT2	8 (4.8)	1 (2.9)	7 (5.3)	
cT3	124 (74.3)	27 (77.1)	97 (73.5)	
cT4	35 (21.0)	7 (20.0)	28 (21.2)	

Clinical N stage				0.13
N0	17 (10.2)	6 (17.1)	11 (8.3)	
N+	150 (89.8)	29 (82.9)	121 (91.7)	
cCR	9 (5.4)	2 (5.7)	7 (5.3)	1.00
Sustained cCR	6 (3.6)	1 (2.9)	5 (3.8)	1.00

Values are given as n (%) or median (range)

BMI, body mass index; TPA, total psoas area; TPAI, total psoas area index; ASA, American Society of Anaesthesiologists; cCR, complete clinical response

Operative findings are summarized in Table 19. There was no significant difference between the groups in procedure, surgical entry, postoperative complications, return to theatre, 30-day readmission, 30-day mortality and length of hospital stay.

Table 19 Operative findings				
Variables	**Total (n=157)**	**Sarcopenic (n=33)**	**Non-sarcopenic (n=124)**	**P value**
Procedure				0.22
Hartmann's	8 (5.1)	3 (9.1)	5 (4.0)	
LAR	10 (6.4)	4 (12.1)	6 (4.8)	
ULAR	79 (50.3)	12 (36.4)	67 (54.0)	
APR	52 (33.1)	13 (39.4)	39 (31.5)	
Proctocolectomy	5 (3.2)	1 (3.0)	4 (3.2)	
Exenteration	3 (1.9)	0 (0.0)	3 (2.4)	
Surgical entry				0.34
Open	145 (92.4)	31 (93.9)	114 (91.9)	
Laparoscopic	4 (2.5)	1 (3.0)	3 (2.4)	
Hybrid	2 (1.3)	1 (3.0)	1 (0.8)	
Robotic	6 (3.8)	0 (0.0)	6 (4.8)	
Postoperative complications				
Anastomotic leak[a]	3 (3.4)	0 (0.0)	3 (4.1)	1.00
Prolonged ileus	41 (26.1)	10 (30.3)	31 (25.0)	0.54
Wound infection	7 (4.5)	1 (3.0)	6 (4.8)	1.00
Overall complications	81 (51.6)	14 (42.4)	67 (54.0)	0.24
Return to theatre	14 (9.0)	3 (9.1)	11 (8.9)	1.00
30-day readmission	7 (4.5)	0 (0.0)	7 (5.7)	0.35
30-day mortality	2 (1.3)	1 (3.0)	1 (0.8)	0.38
Length of hospital stay (days)	10 (4-93)	10 (5-44)	10 (4-93)	0.96

LAR, low anterior resection; ULAR, ultra-low anterior resection; APR, Abdominoperineal resection

[a] Anastomotic leak was calculated including only patients with an anastomosis in the denominator.

Pathological data revealed a good TRG in 9 (27.3%) patients in the SG compared to 54 (43.5%) in the NSG, although the difference was not significantly different (P=0.09). pCR was seen in 4 (12.1%) patients in SG and in 18 (14.5%) patients in the NSG, but this did not reach significance (P=1.00). Assumed CR was found in 5 (14.3%) patients in the SG and 23 (17.4%) patients in the NSG, however there was no significant difference between the groups (P=0.66). There was no significant difference between the groups with respect to pathological T, N, M stage and AJCC stage (Table 20). Univariate analysis revealed BMI≥ 25 kg/m^2 to be the only factor affecting good TRG (P=0.002). Age, BMI, presence of sarcopenia and level of sarcopenic severity were not found to increase the likelihood of pCR and assumed CR (Table 21).

Table 20 Pathological findings				
Variables	**Total (n=157)**	**Sarcopenic (n=33)**	**Non-sarcopenic (n=124)**	**P value**
Pathologic T stage				0.87
ypT0	23 (14.6)	4 (12.1)	19 (15.3)	
ypT1	5 (3.2)	1 (3.0)	4 (3.2)	
ypT2	25 (15.9)	4 (12.1)	21 (16.9)	
ypT3	83 (52.9)	18 (54.5)	65 (52.4)	
ypT4	21 (13.4)	6 (18.2)	15 (12.1)	
Pathological N stage				0.91
ypN0	89 (56.7)	19 (57.6)	70 (56.5)	
ypN1-2	68 (43.3)	14 (42.4)	54 (43.5)	
Pathological M stage				0.95
Mx	13 (8.3)	2 (6.1)	11 (8.9)	
M0	110 (70.1)	24 (72.7)	86 (69.4)	
M1	34 (21.7)	7 (21.2)	27 (21.8)	
Pathologic AJCC stage				0.85
0	22 (14.0)	4 (12.1)	18 (14.5)	
1	20 (12.7)	3 (9.1)	16 (12.9)	
2	36 (22.9)	10 (30.3)	28 (22.6)	
3	45 (28.7)	9 (27.3)	36 (29.0)	
4	34 (21.7)	7 (21.2)	27 (21.8)	
TRG				0.09
TRG 0/1	63 (40.1)	9 (27.3)	54 (43.5)	
TRG 2/3	94 (59.9)	24 (72.7)	70 (56.5)	
pCR				1.00
Yes	22 (14.0)	4 (12.1)	18 (14.5)	
No	135 (86.0)	29 (87.9)	106 (85.5)	
Assumed CR [a]				0.66

Yes	28 (16.8)	5 (14.3)	23 (17.4)	
No	139 (83.2)	30 (85.7)	109 (82.6)	

Values are given as n, n (%) or median (range)

AJCC, American Joint Committee on Cancer; pCR, pathological complete response; TRG, tumour regression grade

[a] The denominator was 167 patients for the total cohort, 33 patients for SG and 124 for the NSG.

Table 21 Univariate regression analysis				
Variables	**Parameter**	**Category**	**Odds ratio (95% CI)**	**P value**
TRG	**Age**	<61 years	Reference	-
		≥ 61 years	0.835 (0.441-1.582)	0.58
	BMI	<25 (kg/m^2)	Reference	-
		≥ 25 (kg/m^2)	3.080 (1.501-6.321)	0.002
	Sarcopenia	No	Reference	-
		Yes	0.486 (0.209-1.131)	0.09
	Severity of sarcopenia			
		Non-sarcopenic	Reference	-
		Mild sarcopenic	0.897 (0.357-2.254)	0.82
		Severe sarcopenic	8.024e^{-10} (0.000)	0.99
pCR	**Age**	<61 years	Reference	-
		≥ 61 years	1.510 (0.605-3.768)	0.38
	BMI	<25 (kg/m^2)	Reference	-
		≥ 25 (kg/m^2)	3.000 (0.963-9.350)	0.06
	Sarcopenia	No	Reference	-
		Yes	0.812 (0.255-2.588)	0.73
	Severity of sarcopenia			
		Non-sarcopenic	Reference	-
		Mild sarcopenic	1.309 (0.397-4.315)	0.66
		Severe sarcopenic	3.645 e^{-9} (0.000)	0.99
Assumed CR	**Age**	<61 years	Reference	-
		≥ 61 years	1.433 (0.632-3.250)	0.39
	BMI	<25 (kg/m^2)	Reference	-
		≥ 25 (kg/m^2)	2.401 (0.915-6.299)	0.08
	Sarcopenia	No	Reference	-
		Yes	0.790 (0.277-2.253)	0.66

	Severity of sarcopenia			
		Non-sarcopenic	Reference	-
		Mild sarcopenic	1.247 (0.422-3.683)	0.69
		Severe sarcopenic	$2.93e^{-9}$ (0.000)	0.99

TRG, tumour regression grade; pCR, pathological complete response

8.5 Discussion

This is the largest study to evaluate whether sarcopenia is a predictor of TRG, pCR and assumed CR in LARC patients undergoing nCRT. The results of this study suggest that sarcopenia was not associated with TRG, pCR and assumed CR. However, BMI≥ 25 kg/m^2 was associated with a good TRG.

The search for risk factors affecting pCR assumes importance given the excellent survival rates for LARC patients with a pCR after nCRT.[325] Several studies have reported on the adverse effects of sarcopenia on overall survival in LARC patients, however the rate of pCR to nCRT has not been adequately examined.[338,339] To date, only one study has described the relationship between sarcopenia and pCR in LARC patients. Olmez et al. showed that sarcopenia along with age, interval time to surgery and level of CEA had a significant effect on pCR. They reported a significantly higher pCR rate in the NSG compared to SG (21.4% vs 3%, P=0.025). In contrast, the pCR rate in our cohort was 14.5% in the NSG compared to 12.1% in the SG, however this was not significantly different (P=1.00). Moreover, on univariate analysis Olmez et al. reported that obesity (BMI≥ 25 kg/m^2) was not a risk factor affecting pCR (P=0.189). Similarly, obesity was not a risk factor affecting either pCR (P=0.06) or assumed CR (P=0.08). The lower rate of stage 3 patients (67.3% vs 89.8%) and smaller sample size (n=61 vs n=167) may have accounted for the discrepancies between Olmez et al. and our findings.

A few studies have reported on the association between obesity and local cancer treatment. Controversy remains as to whether obesity has a harmful effect on pCR rates in LARC patients.[340,341] Our results concur with the findings by Kelady et al. and Olmez et al., where both studies found no significant association between BMI and pCR.[88,333] Nevertheless, we found obesity to have a statistically significant effect on good TRG (P=0.002). We theorise that patients with a higher BMI withstand the weight loss caused by nCRT, whilst underweight patients do not

have an adipose reserve, increasing their risk of complications due to the weight loss. Another possible reason is obesity can result in a state of chronic inflammation which may alter the tumour microenvironment and lead to an increased response to nCRT. Nonetheless, further studies are warranted to investigate the hidden relationship between obesity and improved oncological outcomes.

Several limitations of our study may warrant further investigation. First, the retrospective design and the relatively small sample size may have accounted for some of the observed results. Nevertheless, it remains the largest series to investigate the association between sarcopenia and chemotherapy response in LARC patients. Second, variables such as walking speed, grip strength and fatigue that are synonymous with sarcopenia were not evaluated. Thirdly, 64.4% of non-sarcopenic patients did not have a restaging CT scan making it difficult to draw conclusions regarding the development of post-treatment sarcopenia. Lastly, the recent paradigm shift towards neoadjuvant chemotherapy in TNT type protocols, may further change the parameters and influence the relative importance of sarcopenia in this patient population.

8.6 Conclusion

Sarcopenia is not a predictor of poor nCRT response in LARC patients. Increasing BMI was associated with good TRG in patients with LARC. However, a multicentred study is warranted to validate these findings.

CHAPTER 9: CLINICAL AND BIOCHEMICAL PREDICTORS OF TUMOUR RESPONSE AFTER NEOADJUVANT THERAPY IN RECTAL CANCER.

Statement of Authorship

Title of Paper	Clinical and biochemical predictors of tumour response after neoadjuvant therapy in rectal cancer.
Publication Status	Published
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Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	01/08/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Luke H Traeger		
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Signature		Date	01/08/2022
Name of Co-Author	Tarik Sammour		
Contribution to the Paper	Conception and design of the work Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		
Signature		Date	01/08/2022

9.1 Abstract

Introduction: Patients who have a good clinical and/or pathologic response to neoadjuvant Chemoradiotherapy (nCRT) for rectal cancer have better long-term outcomes and can potentially be spared morbid surgery. This study aimed to identify pre-treatment clinical and biochemical predictors of response to neoadjuvant treatment for rectal cancer.

Methods: Patients undergoing neoadjuvant therapy for rectal cancer between 2007-2022 were retrospectively included. Those patients who achieved a complete clinical response were offered a non-operative management strategy and the remaining patients underwent surgical resection. The primary endpoint was Tumour Regression Grade (TRG) based on radiological imaging (mrTRG) or pathology (pTRG). Patient response was classified as good (mrTRG 1-2 or pTRG 0-1) vs. poor (mrTRG 3-4 or pTRG 2-3). Logistic regression was performed to determine predictors of TRG.

Results: A total of 984 patient with rectal cancer were identified of which 274 met the inclusion criteria. Out of 274 patients, 228 (83%) underwent surgical resection. A good TRG response was observed in 119 (41%) patients and a complete response was achieved in 53 (17%) patients. On univariable and multivariable logistic regression, clinical T2 stage and body mass index of $\geq 25 kg/m^2$ were significant predictors of a good TRG. Clinical T2 stage and a personalised Total Neoadjuvant Therapy (pTNT) regimen were significant predictors of complete response.

Conclusion: Clinical T2 stage and a BMI$\geq 25 kg/m^2$ were predictors of good response to neoadjuvant therapy for rectal cancer. Future prospective studies are required to confirm these findings and evaluate their potential use in better targeting of nCRT.

9.2 Introduction

The standard treatment for Locally Advanced Rectal Cancer (LARC) involves neoadjuvant Chemoradiotherapy (nCRT) followed by Total Mesorectal Excision (TME). This therapeutic strategy has proven to be effective in reducing local recurrence, with potential for organ preservation in the 8-20% of patients who achieve a complete response.[342] However, patients who have a poor response to nCRT, have worse disease free survival, as well as significant long-term morbidity from TME such as urinary and faecal incontinence, and sexual dysfunction.[343,344] Over the last decade, there has been a paradigm shift towards moving the delivery of chemotherapy preoperatively, also referred to as Total Neoadjuvant Therapy (TNT). This approach has significantly higher clinical Complete Response (cCR) and pathological Complete Response (pCR) rates when compared to standard nCRT.[42,130,345]

Determining features that are associated with patient response to nCRT would better inform clinicians and patients the individual prognosis. Several studies have reported clinical factors such as tumour size and type, distance from the anal verge and clinical T and N stage to be predictive of pCR.[71] However, since a pro-inflammatory state has been linked with poor pathological response, studies have begun to investigate haematological and biochemical markers as predictors of response.[346,347] Pre-treatment Carcinoembryogenic Antigen (CEA), neutrophil-lymphocyte, platelet-lymphocyte, lymphocyte-monocyte ratio's and total White Cell Count (WCC) have been associated with cCR after nCRT in rectal cancer.[80,89] However, studies in this area vary considerably with respect to methodology including the number of selected biochemical markers, sample size and definition of outcome variables. Consequently, dependable biochemical factors that allow patients to be counselled in their likelihood of response to neoadjuvant therapy have not yet been adopted into clinical practice.

Given a lack of consensus, and the need for more data, we aim to identify pre-treatment clinical and biochemical variables that predict tumour response to neoadjuvant therapy for rectal cancer in our population using simple and clearly defined measures of response.

9.3 Methods

This retrospective cohort study is reported according to the STROBE (Strengthening The Reporting Observational studies in Epidemiology) statement and was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (HREC/19/CALHN/73) and the St. Andrews Hospital Ethics Committee (#116).[348] This study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was waived for all study participants.

9.3.1 Patients

Patients with biopsy proven rectal adenocarcinoma who received neoadjuvant therapy between January 2007 and August 2022 were retrospectively identified from the Royal Adelaide Hospital and St. Andrews Hospital in South Australia prospectively collected colorectal cancer database. The decision to offer neoadjuvant therapy was made following Multidisciplinary Team (MDT) discussion. Patients treated with palliative intent, received short course radiotherapy, undergoing surgery at other hospitals, non-compliant (did not complete minimum required dose of neoadjuvant therapy) and patients who did not have neoadjuvant therapy were excluded.

9.3.2 Treatment

Two neoadjuvant therapy protocols were used in our institution for the study period (Figure 26). From 2019 onwards, personalized TNT (pTNT) was offered to all rectal cancer patients (induction or consolidation based on initial risk staging). Patients with a need for systemic control (to mitigate risk of distant failure) received induction chemotherapy in the form of 8 cycles 5-Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) over 16 weeks, or 6 cycles Capecitabine and

Oxaliplatin (CAPOX) over 18 weeks. Following induction chemotherapy, patients received long-course nCRT. The neoadjuvant radiotherapy regimen consisted of 50Gy/25 fractions over 6 weeks delivered to the pelvis (rectum and surrounding lymph nodes at risk) with an option for dose escalation to 54Gy/27 fractions using Intensity-Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT). Upon completion of nCRT, patients underwent a 10 week wait period during which oligometastatic resection was performed if indicated. At the end of the wait period patients were restaged with a CT chest/abdo/pelvis, MRI pelvis, and flexible sigmoidoscopy. Patients underwent surgical resection at 10 weeks unless cCR was achieved in which case non operative management was offered. Patients who had loco-regional risk at time of diagnosis, received long course nCRT over 6 weeks, followed by a 2 week wait period. Following this, patients received consolidation chemotherapy over 16 weeks in the form of 8 cycles mFOLFOX6, or 6 cycles CAPOX over 18 weeks. Upon completion of consolidation chemotherapy, patients were restaged with a CT chest/abdo/pelvis, MRI pelvis, and flexible sigmoidoscopy. Patients underwent surgical resection at 4 weeks unless cCR was achieved in which case non operative management was offered.

Prior to 2019, traditional long course nCRT consisted of 45Gy/25 fractions followed by a localized boost of 5.4Gy delivered to the pelvis (rectum and surrounding lymph nodes at risk) over five weeks using IMRT or 3D Conformal Radiation Therapy (3DCRT). Patients concurrently received either continuous infusion of 5-fluorouracil (5-FU) or capecitabine orally five days per week. Surgery was scheduled 8-10 weeks following the radiotherapy for patients who did not achieve a clinical Complete Response (cCR). This was assessed at flexible sigmoidoscopy ± Magnetic Resonance Imaging (MRI) at 8 weeks post completion of nCRT. Following surgery, patients underwent 16 weeks of adjuvant chemotherapy.

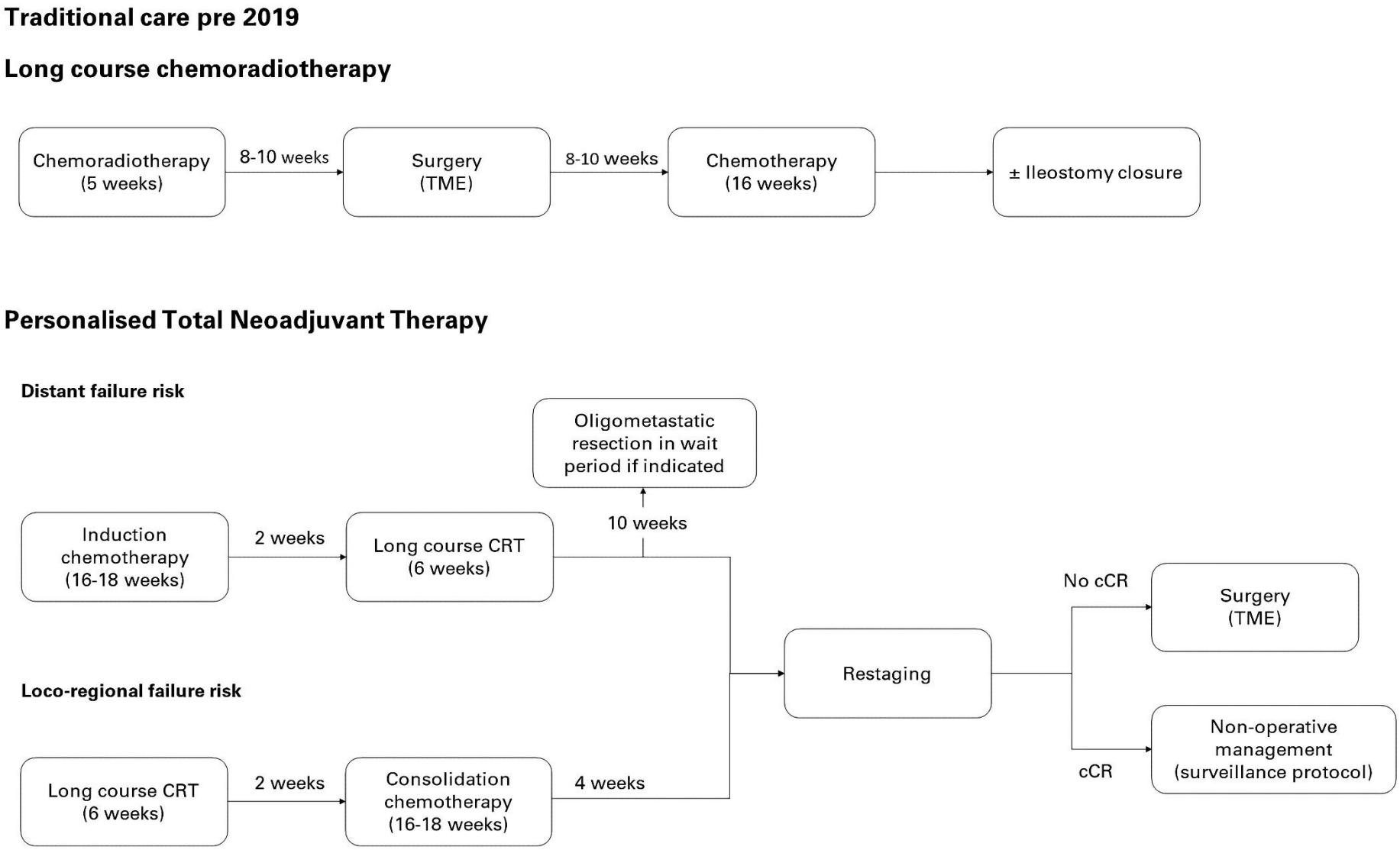

Figure. 26 Neoadjuvant chemoradiotherapy regimens used in this study.

9.3.3 Data collection

The following clinicopathologic variables were obtained from our database: age, gender, Body Mass Index (BMI), sarcopenia (diagnosed using the method proposed by Jones et al.[114]), rectal tumour site, clinical T stage (cT) and N (cN) stage, American Joint Committee on Cancer (AJCC) stage, neoadjuvant therapy regimen, radiotherapy dosage and operation. Race and ethnicity data were not available in our database and are not reported in this study. Biochemical variables were retrospectively collected from routine blood tests were taken from the date closest to the day of diagnosis. Haemoglobin, WCC, platelet, neutrophil, lymphocytes, sodium, potassium, anion gap, glucose, urea, creatine, corrected calcium, albumin, total protein, Lactate Dehydrogenase (LDH) and estimated Glomerular Filtration Rate (eGFR) were collected for each patient. Pathological stage was reported based on the 8th edition of the AJCC Colon and Rectal staging manual.[26]

9.3.4 Outcomes measures

The primary outcome was Tumour Regression Grade (TRG). TRG is a composite measure of MRI tumour regression grade (mrTRG) in non-operative patients and TRG on pathology (pTRG) for operative patients. mrTRG was reported according to the ordinal scale mrTRG 1-5 developed by Patel et al. to assess response on restaging MRI.[232] pTRG was classified based on the AJCC TRG.[349] TRG was categorized based on restaging MRI (mr stage) and / or pathologic assessment of the operative specimen (p stage). A binary classification was defined as good: mrTRG 1-2 and/or pTRG 0-1, or poor: mrTRG 3-5 and /or pTRG 2-3.[337] Patients with a post-treatment response of mrTRG2 and pTRG2 with a long interval (more than 7 weeks) between MRI and surgery were classified as good and those with a short interval (less than 7 weeks) were classified as poor.[350] Secondary outcomes included clinical Complete Response (cCR), pathological Complete Response (pCR), and a composite measure of Complete Response (CR) which included all patient with pCR and cCR with the absence of local regrowth at 2 years follow-up. Patients without a 2-year follow-up were excluded from CR analysis.

9.3.5 Statistical analysis

All analyses were performed using SPSS (IBM, Armonk, NY, USA) version 28. A p-value <0.05 was considered statistically significant. Parametricity was determined using the Shapiro-Wilk test. Normally distributed data were expressed as mean ± SD and nonparametric data as median ± range. Categorical variables were analysed using the Pearson chi-square or Fisher's exact test, where appropriate. Nonparametric continuous variables were analysed with the Mann-Whitney U test, and parametric continuous variables were analysed using the Student's t-test. Missing values were handled using pairwise deletion. Univariable and multivariable logistic regression analysis were used to identify the significant predictors of TRG and CR to neoadjuvant therapy. Receiver Operator Characteristics (ROC) curves were constructed and the Area Under the Curve (AUC) calculated for the combined statistically significant clinical predictors of TRG response and CR.

9.4 Results

9.4.1 Patient characteristics

The study included 254 rectal cancer patients with clinical stage I-IV who underwent neoadjuvant treatment (Figure 27). The median age was 62 (18-96) years old and 65% were male. Patients were commonly non-sarcopenic (74.8%). The tumour was located distally (<8cm on initial staging MRI) in most cases (65.3%), 92% were cT3-4 and 81.4% were clinically node positive (cN+). A total of 193 (70.4%) patients received long-course CRT and 81 (29.6%) patients received pTNT. Patient characteristics for each cohort are summarised in Table 22.

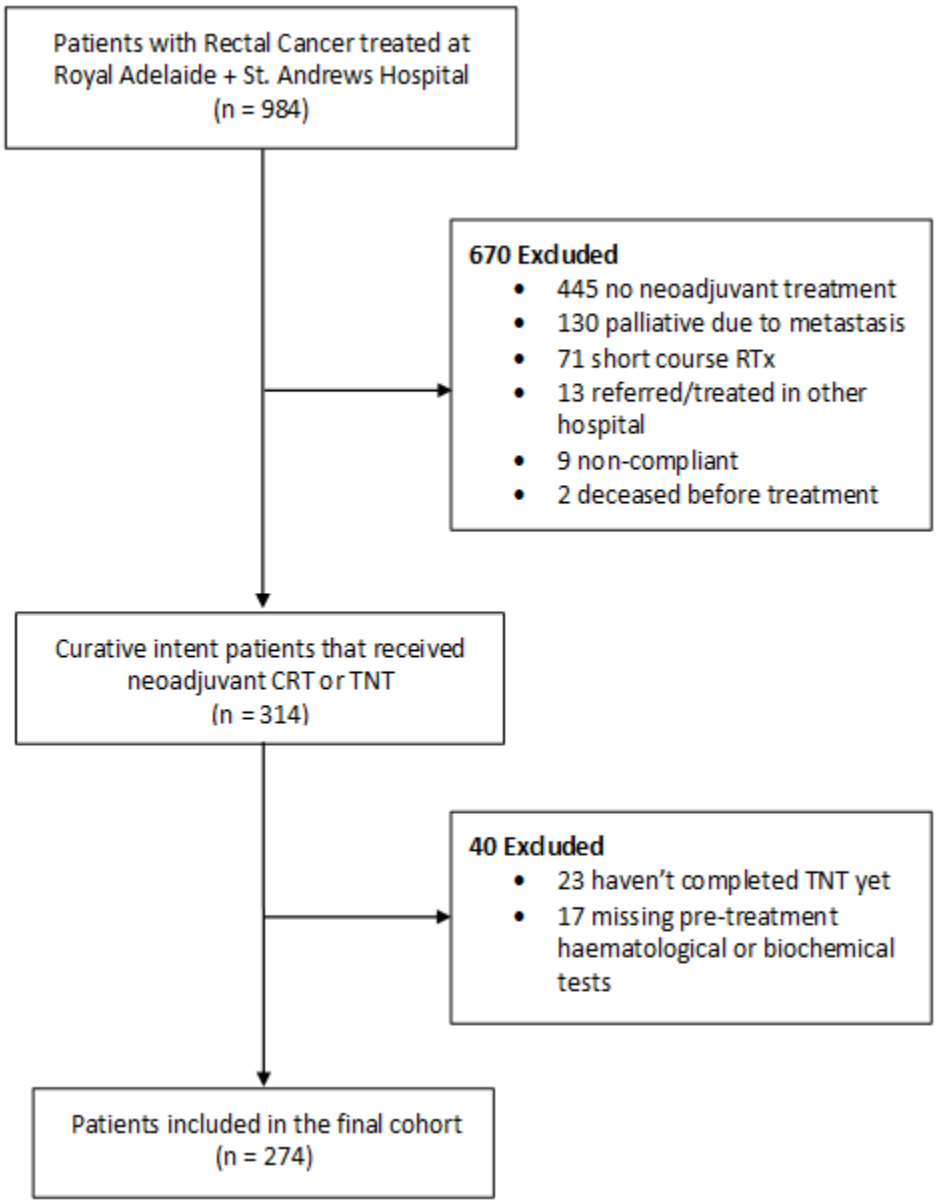

Figure. 27 Patient selection flowchart.

Table 22 Clinicopathological characteristics							
Variable	**Total** (n=274)	**TRG**			**Complete response (sustained cCR + pCR)**		
		Good (n=119)	**Poor** (n=155)	**P**	**Yes** (n=53)	**No** (n=200)	**P**
Age, years	62 (18-96)	60 (23-91)	63 (18-96)	0.101	61 (27-91)	61 (18-96)	0.575
Gender				0.491			0.888
Male	178 (65.0)	80 (67.2)	98 (63.2)		35 (66.0)	130 (65.0)	
Female	96 (35.0)	39 (32.8)	57 (36.8)		18 (34.0)	70 (35.0)	
BMI	26 (13-57)	27 (17-57)	25 (13-44)	<0.001	27 (17-57)	26 (13-44)	0.242
Sarcopenia †				0.010			0.265
Yes	62 (25.2)	18 (17.0)	44 (31.4)		8 (17.0)	44 (24.7)	
No	184 (74.8)	88 (83.0)	96 (68.6)		39 (83.0)	134 (75.3)	
Tumour location				0.424			0.309
High (>12 cm)	19 (6.9)	6 (5.0)	13 (8.4)		3 (5.7)	13 (6.5)	
Medium (8-12cm)	76 (27.7)	31 (26.1)	45 (29.0)		11 (20.8)	62 (31.0)	
Low (<8cm)	179 (65.3)	82 (68.9)	97 (62.6)		39 (73.6)	125 (62.5)	
cT stage				0.004			<0.001
T2	22 (8.0)	16 (13.4)	6 (3.9)		10 (18.9)	9 (4.5)	
T3/4	252 (92.0)	103 (86.6)	149 (96.1)		43 (81.1)	191 (95.5)	
cN stage				0.963			0.750
N0	51 (18.6)	22 (18.5)	29 (18.7)		10 (18.9)	34 (17.0)	
N+	223 (81.4)	97 (81.5)	126 (81.3)		43 (81.1)	166 (83.0)	
AJCC Stage				0.419			0.493
I-II	45 (16.4)	22 (18.5)	23 (14.8)		10 (18.9)	30 (15.0)	
III- IV	229 (83.6)	97 (81.5)	132 (85.2)		43 (81.1)	170 (85.0)	
Neoadjuvant therapy regimen				0.451			0.007
Long-course CRT	193 (70.4)	81 (68.1)	112 (72.3)		33 (62.3)	160 (80.0)	
pTNT	81 (29.6)	38 (31.9)	43 (27.7)		20 (37.7)	40 (20.0)	
RT dosage				0.043			0.194
Received planned RT dose	265 (96.7)	112 (94.1)	153 (98.7)		51 (96.2)	198 (99.0)	
RT boost (≥54Gy)	9 (3.3)	7 (5.9)	2 (1.3)		2 (3.8)	2 (1.0)	

Operation‡				0.140			0.901
Hartmann's	17 (7.5)	3 (3.3)	14 (10.2)		2 (6.1)	15 (7.7)	
LAR/ULAR	178 (78.1)	77 (84.6)	101 (73.7)		29 (87.9)	149 (76.4)	
APR	12 (5.3)	4 (4.4)	8 (5.8)		1 (3.0)	11 (5.6)	
Proctocolectomy	4 (1.8)	2 (2.2)	2 (1.5)		0 (0.0)	4 (2.1)	
Exenteration	16 (7.0)	4 (4.4)	12 (8.8)		1 (3.0)	15 (7.7)	
TEM	1 (0.4)	1 (1.1)	0 (0.0)		0 (0.0)	1 (0.5)	
ypT stage‡				<0.001			<0.001
T0	31 (13.6)	30 (33.0)	1 (0.7)		31 (93.9)	0 (0.0)	
T1	7 (3.1)	3 (3.3)	4 (2.9)		0 (0.0)	7 (3.6)	
T2	36 (15.8)	19 (20.0)	17 (12.4)		0 (0.0)	36 (18.5)	
T3	123 (53.9)	37 (40.7)	86 (62.8)		2 (6.1)	121 (62.1)	
T4	31 (13.6)	2 (2.2)	29 (21.2)		0 (0.0)	31 (15.9)	
ypN stage‡				<0.001			<0.001
N0	142 (62.3)	69 (75.8)	73 (53.3)		32 (97.0)	110 (56.4)	
N+	85 (37.3)	21 (23.1)	64 (46.7)		1 (3.0)	84 (43.1)	
N/A	1 (0.4)	1 (1.1)	0 (0.0)		0 (0.0)	1 (0.5)	

Data are number of patients (%) for categorical variables and mean ± SD/median (range) for continuous variables.

cCR, complete clinical response; pCR, pathological complete response; cT, clinical tumour stage; cN, clinical lymph node stage; BMI, body mass index; CRT, chemoradiotherapy; pTNT, personalized total neoadjuvant therapy; RT, radiotherapy; AJCC, American Joint Committee on Cancer; TEM, Transanal endoscopic microsurgery; LAR, low anterior resection; ULAR, ultra-low anterior resection; APR, abdominoperineal resection; N/A, not applicable.

† Missing sarcopenia measurement n=28

‡ Denominator n= 228

9.4.2 TRG and complete response

A good TRG was seen in 119 (43.4%) patients and 155 (56.6%) patients had a poor TRG. There were 53 (20.9%) who achieved CR and 200 (79.1%) did not achieve CR. On comparative analysis of clinicopathological factors, there was a significant difference between patients classified as having a good TRG from those with a poor TRG in BMI, sarcopenia, cT stage and RT dosage. The factors found to be significantly different between patients that achieved a complete response and those who did not were cT stage and neoadjuvant therapy regimen (Table 22). Table 23 demonstrates biochemical factors for the TRG and complete response groups. Patients with a good TRG were found to have significantly higher median pre-treatment haemoglobin, sodium and albumin levels, along with significantly lower median pre-treatment anion gap and glucose levels. Mean pre-treatment lymphocytes and urea levels were observed to be significantly higher in patients that achieved CR.

Table 23 Pre-treatment biochemical factors compared for TRG response and complete response.						
Variable	**TRG Response**			**Complete response (sustained cCR +pCR)**		
	Good (n=119)	**Poor** (n=155)	**P**	**Yes** (n=53)	**No** (n=200)	**P**
Haemoglobin, g/L	136 (70-180)	130 (73-173)	0.016	132 (78-180)	133 (70-173)	0.773
WCC, $x10^9$/L	7.54 (2.68-16.30)	7.80 (1.60-23.30)	0.232	7.60 (3.14-12.32)	7.70 (1.60-23.30)	0.540
Platelet, $x10^9$/L	284 (70-614)	285 (84-912)	0.596	275 (70-549)	285 (84-912)	0.623
Neutrophils, $x10^9$/L	4.83 (0.23-14.40)	5.28 (1.00-20.26)	0.095	4.58 (2.25-9.18)	5.18 (1.00-20.26)	0.190
Lymphocytes, $x10^9$/L	1.87 (0.22-4.81)	1.74 (0.23-6.61)	0.099	2.06 (0.22-4.61)	1.76 (0.23-6.61)	0.038
Sodium, mmol/L	140 (132-146)	139 (126-146)	0.017	140 (133-146)	140 (126-146)	0.288
Potassium, mmol/L	4.2 (2.9-6.0)	4.2 (2.8-6.3)	0.985	4.1 (3.0-5.3)	4.2 (2.8-6.3)	0.250
Anion gap, mmol/L	13 (5-23)	14 (4-29)	0.027	12 (5-22)	13 (4-29)	0.129
Glucose, mmol/L	5.2 (4-16)	5.6 (2-15)	0.021	5.2 (4-16)	5.4 (2-15)	0.340
Urea, mmol/L	5.3 (1.1-23.8)	5.0 (1.4-20.2)	0.080	5.9 (1.5-23.8)	5.0 (1.1-20.2)	0.005
Creatinine, µmol/L	74 (41-687)	74 (24-657)	0.207	74 (41-687)	74 (24-657)	0.161
Corrected calcium, mmol/L	2.41 ± 0.13	2.42 ± 0.13	0.393	2.42 ± 0.13	2.42 ± 0.13	0.854
Albumin, g/L	38 (24-46)	36 (13-49)	0.009	37 (24-46)	37 (13-49)	0.597
Total protein, g/L	71 (48-87)	71 (40-86)	0.205	72 (51-83)	71 (40-87)	0.167
LDH, U/L	181 (118-399)	186 (87-520)	0.530	192 (118-311)	181 (87-520)	0.383
eGFR, mL/min/1.73m^2			0.721			0.728
>90	41 (34.5)	44 (28.8)		14 (26.4)	61 (30.7)	
60-89	69 (58.0)	93 (60.8)		34 (64.2)	119 (59.8)	
30-59	8 (6.7)	13 (8.5)		4 (7.5)	16 (8.0)	
15-29	0 (0.0)	2 (1.3)		0 (0.0)	2 (1.0)	
<15	1 (0.8)	1 (0.7)		1 (1.9)	1 (0.5)	

Data are number of patients (%) for categorical variables and mean ± SD/median (range) for continuous variables.

pCR, pathological complete response; eGFR, estimated glomerular filtration rate; WCC, white cell count; LDH, lactate dehydrogenase

9.4.3 Univariable and multivariable logistic regression analysis

Variables with statistical differences on comparative analysis were included in the univariable logistic regression (Table 24). Univariable logistic regression analysis revealed that pre-treatment BMI, sarcopenia, cT-stage, haemoglobin, sodium, glucose, anion gap and albumin levels were significantly associated with good TRG. Clinical T-stage, neoadjuvant therapy regimen and urea levels were found to be significantly associated with achieving CR. Multivariable logistic regression analysis revealed BMI≥25kg/m^2 (OR: 1.98; 95%CI: 1.09-3.62; P=0.026) and cT2 (OR: 5.46; 95%CI: 1.62-18.46; P=0.006) to be significantly associated with good TRG. Additional findings from the multivariable logistic regression analysis revealed cT2 (OR: 3.77; 95%CI: 1.38-10.30; P=0.010) and pTNT (OR: 2.10; 95%CI: 1.06-4.15; P=0.034) were significantly associated with achieving CR.

Table 24 Univariable and multivariable logistic regression analysis to identify predictors of TRG response and complete response.

Variables	**Univariable analysis**		**Multivariable analysis**	
	OR (95% CI)	**P**	**Adjusted OR (95% CI)**	**P**
TRG Response				
BMI (kg/m^2), ≥25 vs. <25	2.35 (1.38-4.01)	0.002	1.98 (1.09-3.62)	0.026
Sarcopenia Yes vs. No	0.45 (0.24-0.83)	0.011	0.68 (0.34-1.37)	0.279
cT stage, cT2 vs. cT3/4	3.86 (1.46-10.19)	0.006	5.46 (1.62-18.46)	0.006
RT dosage, boost vs. planned	4.78 (0.98-23.45)	0.054		
Haemoglobin	1.02 (1.00-1.03)	0.011	1.01 (0.99-1.03)	0.196
Sodium	1.10 (1.01-1.20)	0.028	1.02 (0.91-1.13)	0.791
Anion gap	0.93 (0.87-0.99)	0.030	0.937 (0.87-1.02)	0.111
Glucose	0.86 (0.76-0.98)	0.019	0.91 (0.79-1.05)	0.193
Albumin	1.07 (1.02-1.12)	0.003	1.03 (0.96-1.10)	0.459
Complete Response				
cT stage, cT2 vs. cT3/4	4.94 (1.89-12.88)	0.001	3.77 (1.38-10.30)	0.010
Neoadjuvant therapy regimen, pTNT vs. nCRT	2.42 (1.26-4.67)	0.008	2.10 (1.06-4.15)	0.034
Lymphocytes	1.21 (0.87-1.68)	0.249		
Urea	1.12 (1.01-1.24)	0.028	1.10 (0.99-1.22)	0.087

OR, odds ratio; TRG, tumour regression grade; cT, clinical tumour stage; cN, clinical lymph node stage; BMI, body mass index

9.4.4 Multivariable clinical prediction model

Variables with significant predictive values in both univariable and multivariable analysis were combined and evaluated using a ROC analysis (Figure 28). The predictive model based on cT-stage and BMI resulted in an AUC of 0.63 (95%CI 0.56-0.70) for TRG response. The predictive model based on cT- stage and neoadjuvant therapy regimen resulted in an AUC of 0.62 (95%CI 0.53-0.72) for CR.

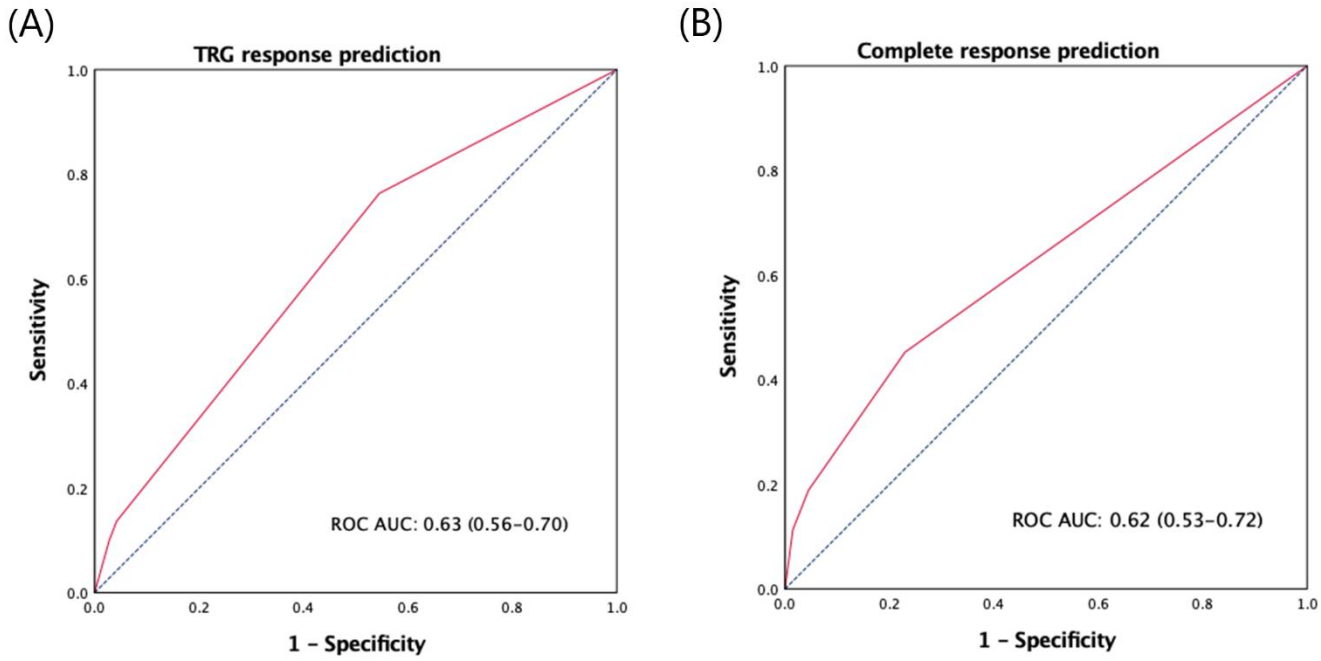

Figure. 28 Receiver operating characteristic curves (ROC) for (A) TRG response and (B) complete response. AUC, area under the curve.

9.5 Discussion

This study investigated a broad range of clinical and biochemical predictors of tumour response in rectal cancer treated with neoadjuvant therapy at two tertiary centres in Australia. Clinical T2 stage and a BMI ≥25kg/m^2 were found to be significant clinical predictors for a good TRG, with an AUC of 0.63. Clinical T2 stage and pTNT were predictive of a CR, with an AUC of 0.62. Interestingly, no pre-treatment biochemical factors were identified on multivariable analysis to be significantly predictive of TRG and CR.

Complete response to neoadjuvant therapy in rectal cancer is associated with excellent long-term outcomes.[342,351] Given this, identifying predictive factors associated with tumour response remain crucial in order to avoid undertreatment in potential responders or overtreating potential non-responders. Fischer et al. evaluated the predictors of pathological response in 164 patients with stage 1-3 rectal cancer.[352] They found low cT stage was associated with good TRG, but not pCR most likely due to their limited sample size. More recently the TRG Snapshot Study Group reported similar results in a cohort of 689 patients with LARC.[353] This study confirms their findings that a low cT stage at diagnosis is associated with a good TRG. The present study found lower cT stage was also associated with an increased CR rate, which is consistent with several previous studies.[80,82,83,354]

A BMI cut-off point of ≥25kg/m^2 was used to categorize obesity in our cohort, which is also consistent with prior studies.[340,355,356] Recently, a meta-analysis has shown specifically in rectal cancer, patients with a BMI≥ 25 were found to have significantly better overall survival compared to patients with a BMI<25.[357] In our cohort, patients with a BMI≥25 achieved a good TRG, and on univariable and multivariable logistic regression it was found to be an independent predictor of good TRG. Consistent with our findings, Lee et al. also showed a BMI≥25 was predictive of pCR in rectal cancer.[340] Nevertheless, it remains unclear why obesity is associated with a good response to

neoadjuvant treatment. One possible reason is excess body fat promotes inflammation and immune cell infiltration, and the interaction between obesity and immune response might alter tumour microenvironment, increasing neoadjuvant treatment response.[358] Another possibility is the hidden mechanism between obesity and molecular signalling pathways, studies have reported that obese patients who expressed nuclear β-catenin were associated with better overall survival.[359] Conversely, recent studies have suggested a BMI≥25 is predictive of poor TRG and pCR to treatment[352,356], with other studies suggesting that BMI was not a predictive factor for pCR.[360,361] Given patients receiving neoadjuvant therapy may have some degree of weight gain or reduction during treatment, BMI can fluctuate during a patients treatment.[352] Regarding the impacts of BMI on treatment adherence and toxicity, Diefenhardt et al. reported that obese patients had worse treatment adherence but less acute organ toxicity if compared to non-obese patients. In their study only 64.4% of obese patients received complete nCRT, seemingly paradoxical given the low toxicity rates, howbeit the data showed dose miscalculation contributed significantly to decreased adherence.[355] Moreover, studies examining the effects of obesity on local recurrence in patients with rectal cancer have published inconsistent results. Some studies have shown obesity leads to increased local recurrence rates due to higher technical difficulty compromising sufficient resection, whereas others failed to confirm this finding.[355,362,363] Given the variety of findings, limited conclusions can be made about the impact of BMI on nCRT outcomes. Furthermore, clinicians should also consider the negative impact a higher BMI has on surgical outcomes.[364]

Studies have highlighted potential shortcomings associated with the administration of adjuvant chemotherapy including poor compliance and no clear survival benefit.[365] pTNT aims to address these challenges by tailoring chemotherapy sequencing to disease risk at presentation which may offer the optimal balance between local and distant disease control whilst improving compliance and tolerability to treatment effects and facilitating organ preservation in select patients.[366] This may explain why in this patient cohort, the CR rate for patients receiving pTNT was 33% compared

with just 17% for those who received nCRT (Table 1; P=0.007). Univariable and multivariable regression analysis confirms this association, with pTNT, there is about a two-fold increase in the odds of achieving a CR in comparison with nCRT. This result corroborates those of previous phase III clinical trials which reported significantly higher rates of CR in the TNT arm in comparison to nCRT arm in patients with LARC.[42,130,345]

It is noteworthy that all patients in our cohort with cCR following neoadjuvant therapy were offered non-operative management. While this is still not considered standard practice in some centres, it is considered a reasonable alternative for rectal cancer patients achieving a cCR after nCRT with similar survival outcomes but superior organ preservation rate as compared to surgery.[324,367,368] Furthermore, prospective data on organ preservation with TNT were recently made available. The OPRA trial showed organ preservation is achievable in 50% of patients with a cCR or near CR with no detriment in survival rates.[42] Ultimately, our non-operative management policy in patients with rectal cancer who had a cCR is feasible, provided patients provide informed consent, and are willing to undergo surveillance as per protocol.[366]

The important limitations of our study include its retrospective design, as well as the relatively small sample size derived from two tertiary centres. Although some missing data could not be avoided, the final dataset was above >98% complete. Over the 13-year period of our study, there has been variability in the neoadjuvant treatment employed, in particular the paradigm shift towards administering pTNT routinely in the latter part of the study. Future prospective studies with larger numbers of patients are required to confirm our findings.

9.6 Conclusion

Clinical T2 stage and a BMI≥25kg/m^2 were predictors of good response to neoadjuvant therapy for rectal cancer. Clinical T2 stage and a pTNT regimen were predictors of CR. Future prospective studies are required to confirm these findings and evaluate their potential use in better targeting of nCRT.

PART 3: ADOPTION OF A PERSONALISED TOTAL NEOADJUVANT THERAPY PROTOCOL FOR THE TREATMENT OF ADVANCED RECTAL CANCER

CHAPTER 10: PERSONALISED TOTAL NEOADJUVANT THERAPY (PTNT) FOR ADVANCED RECTAL CANCER: A PROSPECTIVE COHORT STUDY WITH TAILORED TREATMENT SEQUENCING BASED ON CLINICAL STAGE AT PRESENTATION.

Statement of Authorship

Title of Paper	Personalised Total Neoadjuvant Therapy (pTNT) for advanced rectal cancer with tailored treatment sequencing based on clinical stage at presentation.
Publication Status	Published
Publication Details	Bedrikovetski, S., Fitzsimmons, T., Perry, J., Vather, R., Carruthers, S., Selva-Nayagam, S., Thomas, M.L., Moore, J.W. and Sammour, T. (2022), Personalized total neoadjuvant therapy (pTNT) for advanced rectal cancer with tailored treatment sequencing based on clinical stage at presentation. ANZ Journal of Surgery. https://doi.org/10.1111/ans.18021

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Name of Principal Author (Candidate)	Sergei Bedrikovetski		
Contribution to the Paper	Conception and design of the work Data acquisition Analysis and interpretation of data Drafting the final manuscript		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	01/08/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Tracy Fitzsimmons		
Contribution to the Paper	Conception and design of the work Data acquisition Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		
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Signature		Date	01/08/2022
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Contribution to the Paper	Conception and design of the work Analysis and interpretation of data Drafting significant parts of the final manuscript and critically revising it		
Signature		Date	01/08/2022

10.1 Abstract

Introduction

This study aimed to assess short-term outcomes of a personalised Total Neoadjuvant Treatment (pTNT) protocol, with treatment sequencing based on clinical stage at presentation.

Methods

A multidisciplinary pTNT protocol was implemented across two metropolitan hospitals. This consists of two-schema based on clinical stage: patients with distant failure risk were offered induction chemotherapy before Chemoradiation (nCRT), and patients with locoregional failure risk received nCRT followed by consolidation chemotherapy. Patients underwent surgical resection unless a clinical Complete Response (cCR) was achieved, in which case Non-Operative Management (NOM) was offered. A prospective cohort analysis of all patients with rectal cancer who underwent pTNT with curative intent between Jan 2019 and Aug 2022 was performed.

Results

Of 270 patients referred with rectal cancer, 102 received pTNT with curative intent and 79 have completed their treatment thus far. Thirty-three patients (41.8%) received induction chemotherapy and 46 (58.2%) received consolidation chemotherapy per protocol. The percentage of patients with EMVI, resectable M1 disease, cT4 disease, and positive lateral lymph nodes were 54.4%, 36.7%, 27.8% and 15.2%, respectively. Overall, 32 (40.5%) patients had cCR and 4 (5.1%) pCR, and 40 (50.6%) patients had non-operative management. Grade 3 toxicity was reported in 10.1% of patients and only three patients (3.8%) experienced Grade 4 chemotherapy-related toxicity, with no treatment related mortality.

Conclusion

Early results with a defined two-schema pTNT protocol are encouraging and suggest that tailoring sequencing to disease risk at presentation may represent the optimal balance between local and distant disease control, as well as treatment toxicity.

10.2 Introduction

The standard of care for patients with Locally Advanced Rectal Cancer (LARC) treated with curative intent consists of neoadjuvant long course chemoradiotherapy or short course radiotherapy (nCRT) followed by radical surgery with or without adjuvant chemotherapy.[369,370] This multimodal approach has significantly reduced local recurrence rates from over 30% to approximately 5% over the last several decades.[371] However, rates of distant recurrence have remained relatively recalcitrant, with up to 30% of patient developing distant metastases. This remains the leading cause of rectal cancer-related death.[372] Several trials evaluating the role of adjuvant chemotherapy demonstrated little to no improvement in distant control or survival in LARC patients.[371,373] Notably, only half of eligible patients receive their planned full course adjuvant chemotherapy due to poor compliance, postoperative complications and treatment-related toxicity.[374,375]

Accordingly, there has been a recent shift towards the delivery of chemotherapy pre-operatively, either before (induction) or after (consolidation) nCRT. This is referred to as Total Neoadjuvant Therapy (TNT).[21] This treatment regimen has the potential to improve disease-free survival and reduce the risk of distant failure by improving overall compliance with chemotherapy.[376] Additionally, TNT has the potential to significantly increase pathological Complete Response (pCR) and clinical Complete Response (cCR) rates, with the latter allowing for greater possibility of Non-Operative Management (NOM) and organ preservation.[376,377]

While multiple recent randomised trials have provided supporting data for the safety and effectiveness of TNT,[42,130,345,376,378] the data remain inconclusive regarding optimal sequencing of chemotherapy and radiotherapy. Furthermore, it is unclear whether one form of TNT is suitable for all patients with advanced rectal cancer or whether a risk-adapted treatment strategy based on clinical staging (distant or locally advanced) is more appropriate.[379,380] The aim of this prospective

study was to assess short term outcomes of a personalised Total Neoadjuvant Treatment (pTNT) protocol, with tailored treatment sequencing based on clinical stage at presentation.

10.3 Methods

This prospective cohort study is reported using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[381] and was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (HREC Reference number: HREC/15/RAH/186) and St. Andrew's Hospital Research and Ethics Committee (#117). This study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was provided by each patient.

10.3.1 Patient Selection

All patients with advanced rectal adenocarcinoma within 15cm from the anal verge treated at the Royal Adelaide Hospital (RAH) or St Andrew's Hospital (SAH) from January 1st 2019 to Aug 09st 2022, were prospectively identified. Patients treated who underwent pTNT with curative intent were included in the analysis. The decision to recommend pTNT for advanced rectal cancer was made at a weekly colorectal cancer Multidisciplinary Team meeting (MDT) and followed criteria outlined in a multi-disciplinary protocol designed and implemented *a priori* (Appendix E) and previously reported.[379,382] Patients diagnosed with early stage rectal cancer (T1 or T2, N0, M0) were offered pTNT as an alternative option only if they declined surgery. Patients treated with palliative intent, and those that declined pTNT or were unfit for chemotherapy were excluded. Clinical staging was performed by pelvic Magnetic Resonance Imaging (MRI) and a contrast-enhanced chest-abdomen-pelvis Computed Tomography (CT) as per standard of care practices.

10.3.2 Treatment

The pTNT protocol consists of two distinct treatment schemas, where the sequencing of neoadjuvant treatment was tailored according to patient disease risk based on clinical staging at presentation (Figure. 29). Patients with a high risk of distant failure and a need for prioritisation of systemic disease control (including those with liver or lung metastases, Extramural Vascular Invasion (EMVI) or abnormal mesorectal or lateral pelvic lymph nodes) received induction chemotherapy. This consisted of 8 cycles mFOLFOX6 (5-Fluorouracil [5FU], leucovorin, and oxaliplatin), fortnightly for 16 weeks or 6 cycles of CAPOX (capecitabine and oxaliplatin) for 18 weeks. At the midpoint of induction chemotherapy, a restaging CT was performed and discussed at MDT to identify cases with poor response or disease progression. Following completion of induction chemotherapy and a 2 week wait period, patients received long-course nCRT (50 Gy, 25 fractions) with concurrent 5FU or capecitabine, over 6 weeks. Upon completion of nCRT, patients underwent a 10 week wait period during which oligometastatic resection was performed if indicated. At the end of the wait period patients were restaged with a CT chest/abdo/pelvis, MRI pelvis, and flexible sigmoidoscopy, with a Positron Emission Tomography (PET) scan performed in selected cases. Surgery was performed at 10 weeks if this was indicated based on further MDT discussion.

Patients with a high risk of locoregional failure and a need for local control (including bulky local disease, T4 extension and low tumours) and patients with early-stage disease who declined upfront surgery received consolidation chemotherapy. This involved long-course nCRT administration over 6 weeks, followed by a 2 week wait period. Following this, patients received consolidation chemotherapy for 16 weeks (8 cycles mFOLFOX6, fortnightly for 16 weeks or 6 cycles CAPOX for 18 weeks). At the midpoint of consolidation chemotherapy, a restaging CT was performed and discussed at MDT to identify cases with poor response or disease progression. Upon completion of consolidation chemotherapy, patients were restaged with a CT chest/abdo/pelvis, MRI pelvis, and

flexible sigmoidoscopy with a PET scan performed in selected cases. Surgery was performed at 4 weeks if this was indicated based on further MDT discussion.

In cases with both distant and locoregional failure risk, induction chemotherapy was favoured however this was assessed on a case-by-case basis. Patients underwent surgical resection unless cCR was achieved or patients declined surgery and NOM was offered.

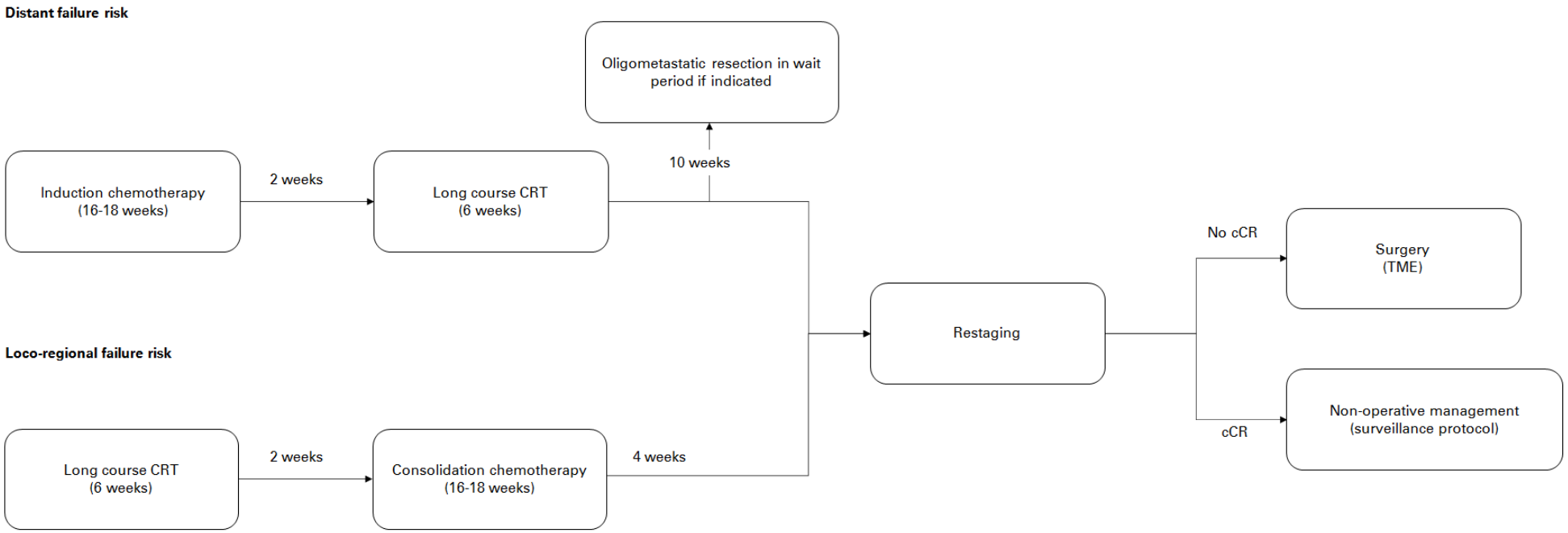

Figure. 29 Personalised total neoadjuvant therapy sequencing. TME, total mesorectal excision.

10.3.3 Endpoints

All data were prospectively collected. The primary endpoint was Complete Response (CR) rate defined as the proportion of patients who achieved either a clinical Complete Response (cCR) or pathological Complete Response (pCR). cCR was defined as the absence of a palpable tumour on digital rectal exam, no visible tumour and the presence of a white scar via flexible sigmoidoscopy, and Tumour Regression Grade (TRG) 1 or 2 on restaging MRI without evidence of abnormal lymph nodes or EMVI.[235] Pathological CR was defined as no residual viable tumour cells detected pathologically (ypT0N0) after surgery.[26,349] Secondary endpoints included distant disease (M1) response defined as complete M1 response, partial M1 response, or progressive M1 disease assessed by specialist radiology review on CT re-staging at MDT. Other secondary endpoints included acute toxicity, compliance, and pathological outcomes. Chemotherapy-related toxicity was graded according to the Common Terminology Criteria for Adverse Events (version 5).[383] Skin toxicity from radiotherapy was graded by the physician according to the Skin Toxicity Assessment Tool (STAT, scale 0-5) and patient using a Patient Symptom Scale (graded as 1 [not at all], 2 [a little], 3 [quite a bit], 4 [very much]) according to the Radiation Induced Skin Reaction Assessment Scale (RISRAS).[384,385] Race and ethnicity data are not routinely collected at our institutions.

10.3.4 Statistical Analysis

Data analysis was performed on an intention-to-treat basis using IBM SPSS Statistics for Macintosh, Version 28.0 (IBM Corp, Armonk, NY, USA). Continous variable parametricity was tested using Shapiro-Wilk test and results are presented as mean ± SD for parametric data and median (range) for nonparametric data.

10.4 Results

10.4.1 Patient characteristics

A total of 270 patients presented with rectal cancer in the 3.7-year study period and 114 were eligible for pTNT after MDT discussion (Figure. 30). Of the 114 patients, 9 refused chemotherapy, two died prior to treatment starting and one the oncologist did not administer the treatment, leaving 102 patients who underwent pTNT. Of these, 79 patients have now completed treatment and restaging (with the rest pending completion). The median follow-up from first MDT date until database lock on August 9th, 2022, was 24 months (range 4-48). The mean age of patients was 60.0 years, with a larger proportion of male patients (65.8%). The median tumour distance from the anal verge was 5.9cm (range 0-14). Approximately one third of patients had potentially resectable stage IV disease at presentation (36.7%). The percentage of patients who had radiological evidence of cT4a, cT4b, EMVI, positive lateral lymph nodes, were 11.4%, 16.5%, 54.4%, 15.2%, respectively (Table 25).

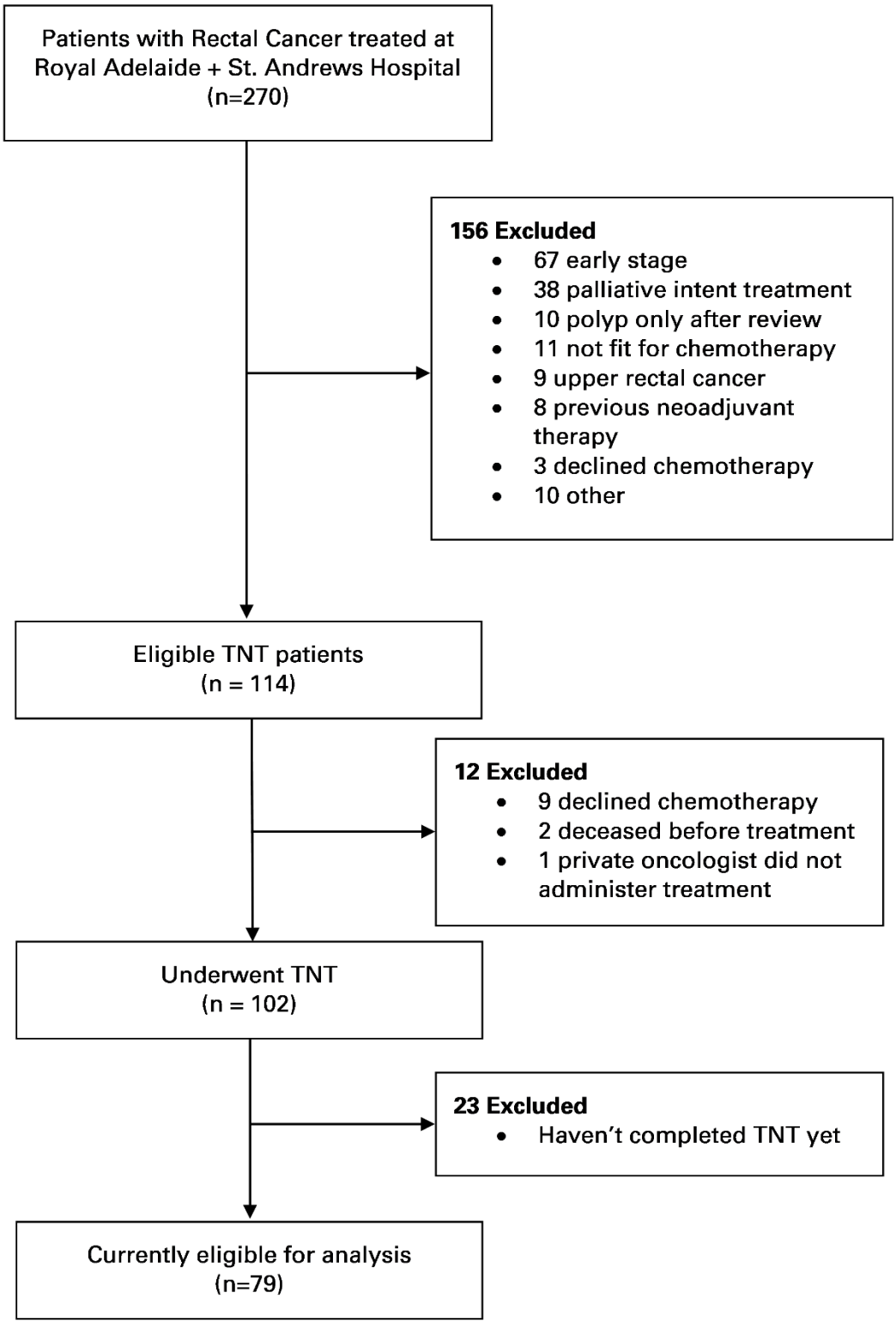

Figure. 30 Patient flowchart.

Table 25 Patient characteristics	
Variable	**N=79** †
Age, years, mean (SD)	60.0 (14.7)
Gender	
Male	52 (65.8)
Female	27 (34.2)
Tumour	
Primary	73 (92.4)
Recurrent	6 (7.6)
ECOG	
0	26 (32.9)
1	28 (35.4)
2	24 (30.4)
3	1 (1.3)
cT stage	
cT2	13 (16.5)
cT3	44 (55.7)
cT4a	9 (11.4)
cT4b	13 (16.5)
cN stage	
cN0	27 (34.2)
cN1	38 (48.1)
cN2	14 (17.7)
cM stage	
M0	50 (63.3)
M1	29 (36.7)
AJCC Stage	
I	8 (10.1)
II	14 (17.7)
III	28 (35.4)
IV	29 (36.7)
Distance to anal verge, cm, median (range)	5.9 (0.0-14.0)
EMVI +ve	43 (54.4)
LPLN +ve	12 (15.2)

ECOG, Eastern Cooperative Oncology Group performance status; AJCC, American Joint Committee on Cancer; LPLN, Lateral Pelvic Lymph Nodes [a] Data are number of patients (%) unless otherwise indicated.

10.4.2 Treatment delivery

Of the 79 patients, 33 (41.8%) received induction chemotherapy and 46 (58.2%) received consolidation chemotherapy (Table 26). Seventy-five patients (94.9%) received long-course nCRT, 3 (3.8%) received short-course nCRT, and one patient did not receive any consolidation chemotherapy due to toxicity during nCRT. Fourty-four (55.7%) patients received CAPOX, 28 (35.4%) received mFOLFOX6, and 7 (8.9%) received other tailored treatment regimens including FOLFIRI, TOMOX, Bevacizumab, Pembrolizumab and Panitumumab. TOMOX was used in one patient with severe coronary artery vasospasm and Bevacizumab / Pembrolizumab / Panitumumab were used as tailored treatment in patients with borderline resectable metastatic disease. Most patients completed the planned number of cycles (73.4%) with a further 24.1% receiving 4 or more cycles of chemotherapy. Only 2 patients (2.5%) received less than 4 cycles due to chemotherapy induced toxicity. Full dose radiotherapy was applied in 74 (93.7%) patients, 3 (3.8%) patients received less than 50Gy and two (2.5%) patients did not receive radiotherapy at all.

Table 26 Treatment delivery, compliance and toxicity	
Variable	**N=79** [a]
pTNT	
Induction	33 (41.8)
Consolidation	46 (58.2)
Chemoradiotherapy	
Long course	75 (94.9)
Short course	3 (3.8)
No chemotherapy	1 (1.3)
Chemotherapy regimen	
mFOLFOX6	28 (35.4)
CAPOX	44 (55.7)
Other	7 (8.9)
Compliance with chemotherapy	
Completed planned cycles	58 (73.4)
≥4 cycles	77 (97.5)
<4 cycles	2 (2.5)
Compliance with radiotherapy	
Received total dose of radiotherapy	74 (93.7)
Radiotherapy discontinuation (total dose <50Gy)	3 (3.8)
No radiotherapy	2 (2.5)
Worst chemotherapy toxicity grade	
No adverse events	10 (12.7)
Grade 1	26 (32.9)
Grade 2	32 (40.5)
Grade 3	8 (10.1)
Grade 4	3 (3.8)
Worst radiotherapy skin toxicity grade	
Physician assessment (scale 0-5)	
No adverse events	39 (49.4)
Grade 1	11 (13.9)
Grade 2	13 (16.5)
Grade 3	11 (13.9)
Grade 4	4 (5.0)

Grade 5	1 (1.3)
Patient assessment (scale 1-4)	
Grade 1	53 (67.1)
Grade 2	12 (15.2)
Grade 3	13 (16.5)
Grade 4	1 (1.3)

pTNT, personalised total neoadjuvant therapy,

† Data are number of patients (%) unless otherwise indicated.

10.4.3 Clinical and pathological response

Overall, 32 (40.5%) patients had cCR and 4 (5.1%) pCR (Table 27). A total of 40 patients (50.6%) opted for non-operative management, 32 of whom achieved a cCR and 8 of whom declined surgery after completing pTNT despite having residual clinical disease. Organ preservation was achieved in 25 (35.2%) out of 71 patients. A total of 38 patients (48.1%) have undergone surgery thus far (Table 28), with a complete locoregional resection (R0) achieved in 89.5%. All patients who underwent surgery had negative distal margins and 4 (10.5%) had positive circumferential margins. Among the 4 patients who had positive circumferential margins, the clinical staging was cT3N0M0, cT3N1M1, cT4bN1M1, cT4bN2M1 and on pathological examination the disease type was found to be ypT3N0 and ypT4bN1 for the remaining 3 patients, respectively. Among the 32 patients in whom cCR was achieved, 6 patients (18.8%) experienced regrowth during the study period and all underwent successful salvage surgery (Table 27). Among the 29 patients who had stage IV disease at presentation, 13 (44.8%) achieved complete M1 response to induction chemotherapy, 6 (20.7%) had a partial M1 response and 10 (34.5%) progressed on treatment. There were 13 patients noted to have a complete response at distant sites, of whom 11 had no detectable lesions on imaging and 2 underwent resection of presumed oligometastatic disease in the wait period with no viable tumour in the specimen. Out of the overall group, 6 have recurred with 3 undergoing oligometastic resection. Currently, 7 patients are currently disease free under surveillance. Among the 50 patients who had stage I-III disease at presentation, 27 (54.0%) achieved a local CR (pCR and / or cCR), 23 (46.0%) had a local partial response and no patients had distal progression.

Among the 9 patients with cT4a disease, 4 achieved a cCR, 3 proceeded to radical resection, 1 declined surgery, and 1 died as a result of progression on treatment. Among the 13 patients with cT4b disease, 3 achieved a cCR, 8 underwent pelvic exenteration procedures, 1 declined surgery, and 1 was deemed medically unfit for surgery. There were 12 patients with clinical LPLN

involvement, of whom 10 completely responded on MRI, 2 did not respond to treatment and underwent LPLN dissection.

Table 25 Response to treatment	
Variable	**N=79**[†]
CR (pCR and / or cCR)	
Yes	35 (44.3)
No	43 (54.4)
N/A	1 (1.3)
cCR	
Yes	32 (40.5)
No	46 (58.2)
N/A	1 (1.3)
M1 Response[‡]	
Complete	13 (44.8)
Partial	6 (20.7)
Progressed	10 (34.5)
NOM	
Yes	40 (50.6)
No	39 (49.4)
Regrowth[§]	
Yes	6 (18.8)
No	26 (81.2)

CR, complete response; cCR, clinical CR; NOM, non-operative management

[†] Data are number of patients (%) unless otherwise indicated.

[‡] M1 response was calculated including only patients with distant metastasis in the denominator.

[§] Regrowth was calculated including only patients with cCR in the denominator.

Table 26 Surgical and pathological characteristics	
Variable	**N=38**[†]
Type of surgery	
Hartmanns	6 (15.8)
LAR/ULAR	15 (39.5)
APR	4 (10.5)
Proctocolectomy	1 (2.6)
Pelvic Exenteration	11 (28.9)
Defunctioning colostomy	1 (2.6)
Completeness of tumour resection	
R0	34 (89.5)
R1	2 (5.3)
R2	2 (5.3)
Mesorectal grade	
1	1 (2.6)
2	2 (5.3)
3	33 (86.8)
N/A	2 (5.3)
CRM <1mm	4 (10.5)
DRM <1mm	0 (0.0)
ypT stage	
ypT0	5 (13.2)
ypT1	1 (2.6)
ypT2	6 (15.8)
ypT3	20 (52.6)
ypT4a	1 (2.6)
ypT4b	4 (10.5)
N/A	1 (2.6)
ypN Stage	
ypN0	26 (68.4)
ypN1	8 (21.1)
ypN2	3 (7.9)
N/A	1 (2.6)
pCR	
Yes	4 (10.5)

No	34 (89.5)
Stoma	
End colostomy	21 (55.3)
Loop Ileostomy	16 (42.1)
End ileostomy	1 (2.6)
Loop ileostomy closure‡	
Yes	13 (81.3)
No	3 (18.7)
Months to ileostomy closure, Mean (SD)	3.9 (1.2)

LAR, low anterior resection; ULAR, ultra-low anterior resection; APR, abdominoperineal resection; CRM, circumferential resection margin; DRM, distal resection margin; pCR, pathological complete response

† Data are number of patients (%) unless otherwise indicated.

‡ Loop ileostomy closure was calculated including patients with a loop ileostomy in the denominator.

10.4.4 Toxicity

Chemotherapy-related toxicity was experienced by 87.3% of patients with the majority being Grade 1 (32.9%) and 2 (40.5%, Table 26). Grade 3 toxicity was reported by 10.1% of patients and only three patients (3.8%) suffered Grade 4 chemotherapy-related toxicity (severe enterocolitis in one and febrile neutropenia in two patients). Radiotherapy-related toxicity was reported in 50.6% and 32.9% of physician and patient reporting measures, respectively. Four patients (5.0%) were assessed by the treating physician as having Grade 4 and one (1.3%) patient as having Grade 5 radiotherapy-related toxicities (all skin related). Only one patient (1.3%) reported Grade 4 radiotherapy-related toxicity (skin tenderness) as assessed on the Patient Symptom Scale. Six patients (7.6%) died as a result of advanced rectal cancer during the study period.

10.5 Discussion

In this study, we report early results of a tailored TNT protocol for advanced rectal cancer, with treatment sequencing based on clinical staging at presentation. Over 40% of all patients demonstrated complete response in the primary tumour site, with a resulting high rate of organ preservation despite an at-risk patient population and advanced disease at baseline. Additionally, complete M1 response was observed in just under half of patients with resectable stage IV disease, and these patients avoided oligometastatic resection. The toxicity profile was better than expected compliance with chemotherapy was high, and there was no treatment related mortality. To our knowledge, this is the first study reporting outcomes from a two-schema personalised TNT protocol, and the first Australian study reporting short term outcomes of TNT.

The current findings are consistent with previous publications demonstrating relatively high rates of primary tumour response and compliance with chemotherapy for TNT in comparison with standard neoadjuvant treatment.[386-388] At the time of introduction of our protocol there was a paucity of level 1 evidence for TNT, given the four randomised controlled trials had not been published in full

yet.[130,345,378,389] To account for this, we employed an integrated approach across disciplines with justification based on level 2 data, ethics committee approval, and rigorous prospective data collection with frequent reporting of outcomes.

There are now multiple published randomised controlled trials investigating TNT.[130,345,378,389] Rapido and PRODIGE 23 randomised patients to consolidation TNT vs standard long course neo-adjuvant nCRT (short course TNT in the former, and long course TNT in the latter).[345,389] Both studies mandated surgery regardless of response and demonstrated significantly higher rates or pCR and improved disease-free survival with TNT without significantly increased in toxicity. Importantly, compliance with chemotherapy was high (85% in Rapido, and 92% in PRODIGE23) but with relatively high rates of grade 3-4 toxicity (48% in RAPIDO and 46% in PRODIGE23).[390,391] Undoubtedly, excess toxicity is a consideration with TNT. However, it is argued that a substantial number of patients treated with standard pathways do not receive their adjuvant chemotherapy (92% TNT group versus 75% standard care group in PRODIGE23). The standard care group in PRODIGE23 experienced more serious adverse events during adjuvant therapy than the neoadjuvant chemotherapy group. Also importantly, most randomised phase III trials conducted in rectal cancer have shown little to no benefit for adjuvant chemotherapy.[392] Taken together, these data indicate that delivering systemic chemotherapy pre- rather than post-operatively not only improves oncological outcomes, but also allows us to spare patients from unnecessary toxicities derived from ineffective postoperative therapies.[393]

Chemotherapy related toxicity appears to be lower with induction compared with consolidation protocols, at the expense of lower primary response rates. The CAO/ARO/A10-12 study randomised 306 patients to receive induction or consolidation chemotherapy and all underwent surgery regardless of tumour response.[378] Patients treated with consolidation chemotherapy had higher pCR rates (25% vs 17%) but suffered more grade 3-4 toxicity (37% vs 27%) and lower rates

of compliance with chemotherapy (85% vs 92%, respectively). Conversely, compliance with radiotherapy was better in the consolidation arm (97% vs 91%). The limitations of CAO/ARO/A10-12 study are that only 3 cycles of FOLFOX were given pre-operatively, and that oxaliplatin was routinely used as a radiosensitiser with long course radiotherapy (not routine practice in most centers).[387,394] The more recent OPRA trial, randomised 324 patients to induction or consolidation chemotherapy followed by either TME or a selective NOM approach on the basis of tumour response.[42] The was no difference in the rate of 3-year disease free survival between treatment groups. Patients treated with consolidation had higher organ preservation rates (60% vs 47%), but lower rates of compliance with chemotherapy (94% vs 99%) and higher rates of compliance with radiotherapy (98% vs 93%, respectively) consistent with results of the CAO/ARO/AIO-12 trial. Chemotherapy toxicity rates were not reported separately, but these results suggest that compliance with components of TNT is better with whatever treatment is give first (chemotherapy or radiotherapy) further supporting the idea that the most important treatment should be prioritised based on disease risk profile.

It is clear from the data above that, compared with standard care, TNT offers better rates of primary tumour response, organ preservation and disease free survival in patients with locally advanced rectal cancer.[378,389,391,395] However, while optimal treatment sequencing is yet undefined, consolidation chemotherapy likely offers improved primary response rates but at the expense of increased chemotherapy toxicity (and therefore compliance).[378,380] Therefore, it may be rational to tailor the order of TNT to disease biology.[133,134] In the current study, a two-schema approach to TNT treatment addresses sequence administration by considering tumour biology and patient disease risk profile at presentation and attempts to prioritise compliance with the most vital component of TNT treatment. Despite inclusion of a broad, unselected group of real-world patients with high-risk disease, we found a relatively lower rate of toxicity than previously reported with TNT, and equivalent outcomes in terms of compliance and response.[378,389,391,395]

Local regrowth rate is an important concern in patients with cCR who undergo the NOM approach. However, salvage surgery is appropriate and based on current evidence appears to achieve similar rates of DFS and OS as upfront surgery.[396,397] The local regrowth rate in this study was consistent with previous studies and all patients were salvageable with radical resection.[396,398] Although some studies currently suggest local excision, TME remains the treatment of choice in our unit in the case of local regrowth.[87,399]

The current study is limited by the short duration of follow-up, and long-term data is required to confirm safety and efficacy of this tailored approach. This will be the subject of further analysis on data maturity. The current study design included all patients with advanced rectal cancer treated with curative intent, including those with resectable oligometastatic disease. This limits comparisons to previously published data (including all four RCTs that only included stage II/III patients). However, the authors feel that this population better reflects of the reality of TNT administration in practice and provides a more comprehensive insight into the merits of induction chemotherapy as part of a risk adapted TNT treatment strategy. Furthermore, it is not clear that a single liver metastasis, for example, represents higher risk than extensive EMVI, with both representing high risk of distant failure with standard treatment paradigms. The study did not include a comparison group, but again we intend this to be the subject of a future study using a matched historical cohort with standard care once there are enough patients included for such a study to be adequately powered.

10.6 Conclusion

Early results with a defined two-schema pTNT protocol are encouraging and suggest that tailoring sequencing to disease risk at presentation may represent optimal balance between local and distant disease control. Long-term data are required to determine the effect of pTNT on disease-free, local recurrence and overall survival rates.

CHAPTER 11: TOTAL NEOADJUVANT THERAPY VS CHEMOTHERAPY DURING THE 'WAIT PERIOD' VS STANDARD CHEMORADIOTHERAPY FOR LOCALLY ADVANCED RECTAL CANCER.

Statement of Authorship

Title of Paper	Personalised total neoadjuvant therapy vs chemotherapy during the 'wait period' vs standard chemoradiotherapy for locally advanced rectal cancer.
Publication Status	Published
Publication Details	Bedrikovetski S, Traeger L, Fitzsimmons T, Perry J, Vather R, Moore JW, Sammour T. Personalized total neoadjuvant therapy versus chemotherapy during the 'wait period' versus standard chemoradiotherapy for locally advanced rectal cancer. ANZ J Surg. 2022 Dec 27. doi: 10.1111/ans.18229. Epub ahead of print. PMID: 36573638.

Principal Author

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Contribution to the Paper	Conception and design of the work Data acquisition Analysis and interpretation of data Drafting the final manuscript		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	01/08/2022

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Signature		Date	01/08/2022

11.1 Abstract

Background: This study aimed to compare current treatment response rates with personalised Total Neoadjuvant Therapy (pTNT), against extended chemotherapy in the 'wait period' (xCRT) and standard Chemoradiotherapy (sCRT) with adjuvant chemotherapy for rectal cancer.

Methods: This was a multicentre retrospective cohort analysis. Consecutive patients with rectal cancer treated with pTNT over a 3.9-year period were compared to a historical cohort of patients treated with xCRT or sCRT as part of the published WAIT Trial. pTNT patients received 8 cycles mFOLFOX6 or 6 cycles CAPOX in the neoadjuvant setting (no adjuvant treatment). Patients in the WAIT Trial received either 3 cycles 5-FU/LV during the 10-week wait period after chemoradiotherapy or standard chemoradiotherapy, followed by adjuvant chemotherapy. The primary endpoint was overall Complete Response (oCR) rate defined as the proportion of patients who achieved either clinical Complete Response (cCR) or pathological Complete Response (pCR).

Results: Of 284 patients diagnosed with rectal cancer during the 3.9-year period, 107 received pTNT. Forty of these were matched with 49 patients from the WAIT Trial (25 received xCRT and 24 received sCRT). There was a significant difference in oCR between the groups (pTNT n=21, xCRT n=6, sCRT n=7, P=0.043). Of the patients that underwent surgery, pCR occurred in 13 patients with no significant difference between groups (P=0.415). There were no significant differences in 2-year disease-free survival or overall survival.

Conclusion: Compared with sCRT and xCRT, pTNT results in a significantly higher complete response rate which may facilitate organ preservation.

11.2 Introduction

The current standard treatment regimen for patients with Locally Advanced Rectal Cancer (LARC) consists of neoadjuvant Chemoradiotherapy (sCRT) followed by surgical resection with Total Mesorectal Excision (TME) and adjuvant chemotherapy.[320] While this multimodal approach has significantly reduced local recurrence from 30% to less than 5%, distant recurrence occurs in approximately 30% of patients and remains the leading cause of cancer-related death in LARC patients.[35,400,401] The role of adjuvant chemotherapy remains controversial, as studies have not demonstrated a significant improvement in Disease Free Survival (DFS) or Overall Survival (OS). This is likely due to poor compliance, delays from time of diagnosis to commencement of adjuvant chemotherapy and suboptimal chemotherapy dosing.[375,402] A 4-week delay in adjuvant treatment has been associated with a 14% decrease in OS.[403,404]

Total Neoadjuvant Therapy (TNT) is a relatively new treatment paradigm, where the chemotherapy is brought forward to the neoadjuvant period, either prior to sCRT (induction) or after sCRT (consolidation), with the aim of treating micrometastasis prior to definitive surgery. This protocol has the potential to increase compliance to systemic chemotherapy and DFS. Recently, two Randomised Controlled Trials (RCT) reported higher pathological Complete Response (pCR) rates and a lower distant recurrence rate with TNT compared to sCRT.[130,345] Additionally, TNT has been shown to increase the proportion of patients achieving a clinical Complete Response (cCR) allowing for Non-Operative Management (NOM) and organ preservation.[42,387] Despite the potential advantages of TNT, it remains unclear if TNT benefits all patients with LARC, if it improves overall survival, or whether treatment sequencing should be tailored towards risk for developing local or distant recurrence at presentation.[133]

In 2019, two metropolitan hospitals in Adelaide, South Australia adopted a personalised TNT (pTNT) protocol comprising a risk-adapted treatment strategy based on clinical staging (distant or

locally advanced) at presentation whereby those at risk of distant failure (EMVI +ve, cN+ve, M1) underwent induction chemotherapy while those at risk of local failure (cT3/4) underwent consolidation chemotherapy.[132] Prior to this, a locally run randomised control trial (WAIT trial) evaluated the addition of three cycles of 5-fluorouracil/leucovorin during the 10 week wait period after sCRT and reported similar pCR rates to sCRT alone in patients with LARC.[405] Here, we aim to compare current treatment response rates with pTNT versus extended chemoradiotherapy (xCRT) in the 'wait period' or sCRT.

11.3 Materials and Methods

This multicentre retrospective cohort analysis is reported using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (HREC Reference number: HREC/15/RAH/186) and St. Andrew's Hospital Research and Ethics Committee (#117). Informed consent was provided by all patients according to the ethical standards of the Helsinki Declaration of 1975.

11.3.1 Patient Selection

Prospective data of patients with LARC who underwent pTNT from January 2019 to October 2022 were compared to a historical cohort of patients who received xCRT or sCRT from April 2012 to June 2014 in the WAIT trial.[131,405] Analysis was limited to patients in the pTNT cohort who met the eligibility criteria for the WAIT trial. This included patients diagnosed with LARC located within 12cm from the anal verge, defined as clinical stage T3/4 or any node positive disease. Local staging was determined based on pelvic Magnetic Resonance Imaging (MRI) and contrast-enhanced chest-abdomen-pelvis Computed Tomography (CT) evaluated distant disease. Patients were excluded if they were <18 or >80 years old, had Metastatic disease (M1) at presentation, or did not undergo neoadjuvant treatment.

11.3.2 Treatment

Groups were determined based on the neoadjuvant treatment regimen received (Figure. 31). From 2019 onwards, pTNT was offered to all rectal cancer patients (induction or consolidation based on risk of locoregional or distant failure) without adjuvant treatment. Patients at risk of distant failure (including those with liver or lung metastases, Extramural Vascular Invasion (EMVI) or abnormal mesorectal or lateral pelvic lymph nodes) received induction chemotherapy. This consisted of 8 cycles mFOLFOX6 (5-Fluorouracil [5-FU], leucovorin, and oxaliplatin), fortnightly for 16 weeks or 6 cycles of CAPOX (capecitabine and oxaliplatin) for 18 weeks. Following completion of induction chemotherapy and a 2 week wait period, patients received long-course CRT consisting of 50Gy/25 fraction (option for dose escalation 50.4Gy/27 fractions) with concurrent intravenous 5FU or oral capecitabine, over 6 weeks. After completion of CRT, patients underwent a 10-week wait period in which oligometastatic resection was performed if indicated. At the end of the wait period patients were restaged with a CT, MRI, and flexible sigmoidoscopy.

Patients with a high risk of locoregional failure (including bulky local disease, T4 extension and low tumours), received long course CRT over 6 weeks, followed by consolidation chemotherapy over 16 weeks consisting of 8 cycles mFOLFOX6, or 6 cycles CAPOX over 18 weeks. Upon completion of consolidation chemotherapy, patients were restaged with a CT, MRI, and flexible sigmoidoscopy. Patients who achieved a cCR were offered NOM, the remaining proceeded to surgical resection. In cases with both distant and locoregional failure risk, induction chemotherapy was favoured however this was assessed on a case-by-case basis.

Between 2012-2014 as part of the WAIT trial, all patients underwent long-course CRT consisting of 45Gy/25 fractions (option for dose escalation to 50.4Gy/28 fractions) with concurrent intravenous 5-FU, over five weeks. For patients in the sCRT group, no further neoadjuvant chemotherapy was administered. Patients in the xCRT group received further chemotherapy comprising of 3 cycles of

bolus 5-FU with leucovorin on each of 3 days, 3 weekly. Surgery was scheduled 10 weeks after completion of radiotherapy with the addition of adjuvant chemotherapy if clinically indicated. During this time, NOM was not included in the treatment protocol for patients who achieved a cCR within the participating hospitals.

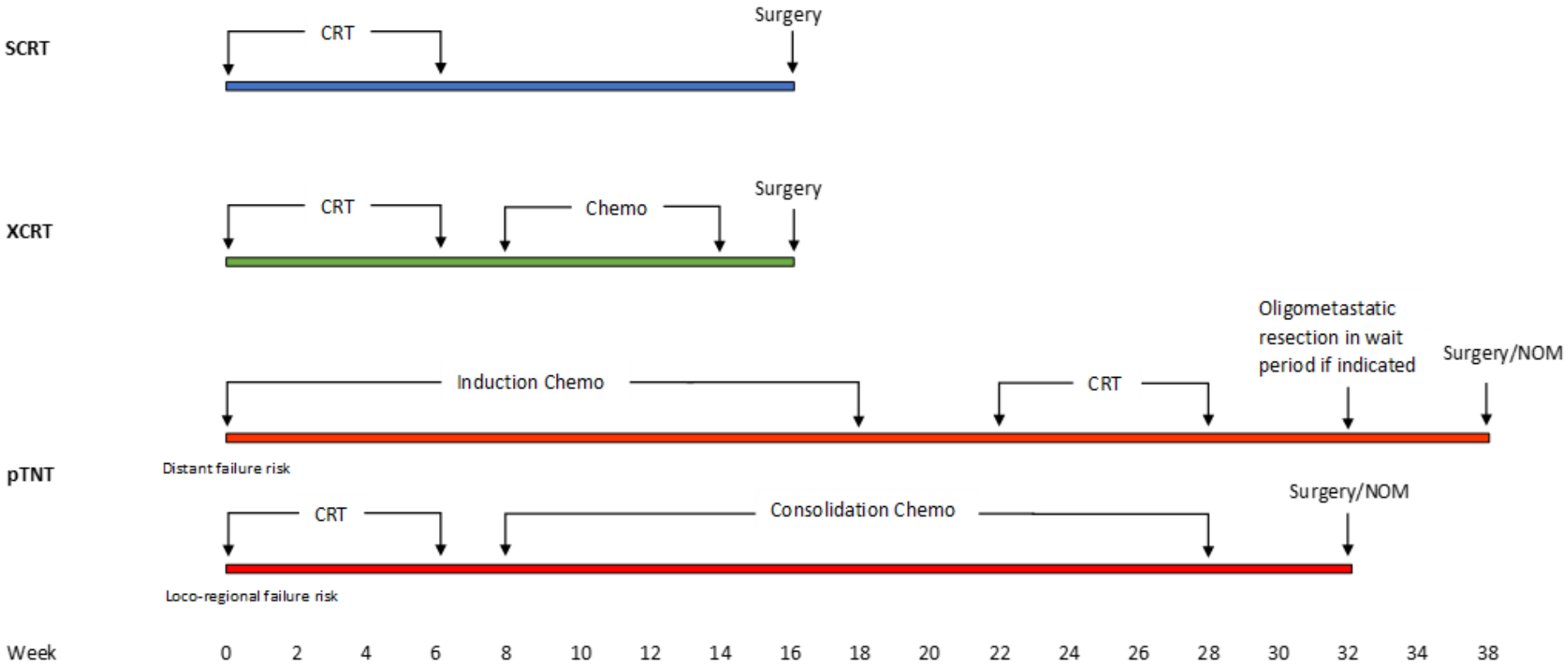

Figure. 31 Schema of the four neoadjuvant therapy approaches. sCRT, standard long-course chemoradiotherapy; xCRT, extended chemotherapy; pTNT, personalised total neoadjuvant therapy.

11.3.3 Endpoints

The primary endpoint was overall Complete Response (oCR) defined as the proportion of patients who achieved either a cCR or pCR. pCR was defined as no residual tumour cells in the surgical specimen.[26,349] In the pTNT group, cCR was routinely assessed at the end of treatment and defined as the absence of a palpable tumour on digital rectal exam, no visible tumour and the presence of a white scar via flexible sigmoidoscopy, as well as Tumour Regression Grade (TRG) 1 or 2 on restaging MRI without evidence of abnormal lymph nodes or EMVI.[235] In the sCRT and xCRT groups, cCR was assessed if there was absence of macroscopic tumour at the primary tumour site on digital rectal exam and endoscopy. Secondary endpoints included 2-year DFS, 2-year OS, pathological and surgical outcomes as well as 30-day postoperative complications, graded according to the Clavien-Dindo (CD) classification.[406] The quality of mesorectal excision was assessed by pathologists using Quirke's method and Tumour Regression Grade (TRG on pathological assessment) was classified based on the American Joint Committee on Cancer (AJCC).[26,406,407]

11.3.4 Statistical Analysis

Parametricity was determined using the Shapiro-Wilk test. Normally distributed variables were expressed as mean (standard deviation) and nonparametric variables as median (range). Categorical variables were presented as frequencies and percentages. Continuous variables were compared using ANOVA or Kruskal-Wallis test depending on the type of distribution. Categorical variables were compared using χ^2 or Fisher's exact test. DFS and OS were analysed separately using the Kaplan-Meier method and log-rank tests. A P-value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Macintosh, version 28 (IBM Corp., Armonk, N.Y., USA).

11.4 Results

11.4.1 Patient characteristics

Between January 2019 and September 2022, 284 patients presented with rectal cancer and 107 underwent pTNT. Of these, 40 patients fulfilled the inclusion criteria, and were compared with 49 patients from the WAIT Trial (25 received xCRT and 24 received sCRT) (Figure 32). Baseline patient demographics and tumour characteristics are listed in Table 29. Although baseline patient and tumour characteristics were largely similar, there were some notable differences among the groups. The percentage of patients in the pTNT group with cN0 and American Society of Anaesthesiologists grade 3-4 were significantly higher compared with xCRT and sCRT groups (30.0% vs 0% vs 8.3%, P<0.001; 73.9% vs 28% vs 20.8%, P=0.0003), respectively.

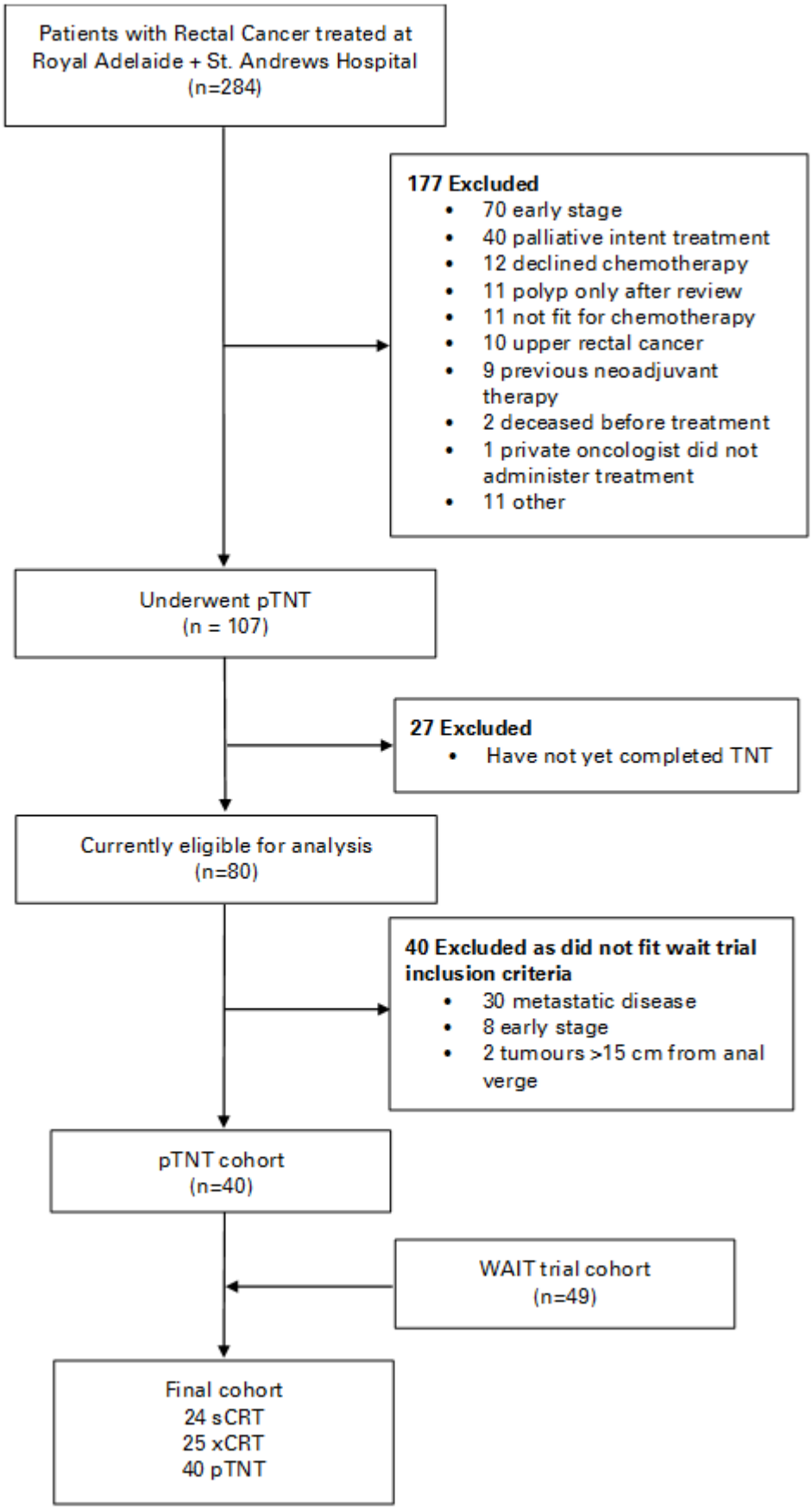

Figure. 32 Patient flowchart.

Table 29 Baseline patient and tumour characteristics				
	sCRT **N= 24**	**xCRT** **N=25**	**pTNT** **N=40**	**P-value**
Age, years (Mean±SD)	60.4±12.5	59.7±10.1	59.2±13.0	0.937
Gender (Male: Female)	18:6	18:7	26:14	0.970
BMI (kg/m^2)	26.8±4.3	26.0±3.5	28.8±10.3	0.367
Distance from anal verge (cm)	6.0±2.6	6.6±2.6	5.7±3.0	0.435
Clinical stage				
cT2	1 (4.2)	0 (0.0)	2 (5.0)	0.236
cT3	18 (75.0)	24 (96.0)	31 (77.5)	
cT4	5 (20.8)	1 (4.0)	7 (17.5)	
cN0	2 (8.3)	0 (0.0)	12 (30.0)	**<0.001**
cN1	7 (29.2)	6 (24.0)	23 (57.5)	
cN2	15 (62.5)	19 (76.0)	5 (12.5)	
CRM				0.350
Clear	12 (50.0)	10 (40.0)	15 (37.5)	
Threatened	4 (16.7)	8 (32.0)	6 (15.0)	
Involved	8 (33.3)	7 (28.0)	19 (47.5)	
EMVI				0.676
Positive	8 (33.3)	11 (44.0)	22 (55.0)	
Negative	16 (66.7)	14 (56.0)	18 (45.0)	
ASA score[†]				**0.0003**
1-2	19 (79.2)	18 (72.0)	6 (26.1)	
3-4	5 (20.8)	7 (28.0)	17 (73.9)	

ASA, American Society of Anaesthesiologists; BMI, body mass index; CRM, circumferential radial margin; EMVI, extramural vascular invasion.

[a] 23 out of 40 patients underwent surgery in the pTNT group

11.4.2 Response to treatment and survival outcomes

The oCR (cCR and/or pCR) rate was significantly higher in the pTNT group compared with xCRT and sCRT (52.5% vs 24.2% vs 29.2%, P=0.043; Table 30). In addition, cCR rate in the pTNT group was significantly increased compared to xCRT and sCRT groups (47.5% vs 12% vs 8.3%, P<0.001). There was no significant difference in pCR rate between the groups (pTNT n=3 (13.0%), xCRT n=4 (16.0%), sCRT n=6 (25.0%), P=0.553). There were no significant differences in 2-year DFS rates between the groups (pTNT n=22 (91.7%), xCRT n=19 (76%), sCRT n=19 (79.2%), P=0.249). The 2-year OS also did not differ between the groups (pTNT n=23 (95.8%), xCRT n=21 (84.0%), sCRT n=23 (95.8%), P=0.182) (Figure 33).

Table 30 Response to treatment				
	sCRT **N= 24**	**xCRT** **N=25**	**pTNT** **N=40**	**P-value**
oCR (pCR and / or cCR)	7 (29.2)	6 (24.2)	21 (52.5)	**0.043**
cCR	2 (8.3)	3 (12.0)	19 (47.5)	**<0.001**
pCR[†]	6 (25.0)	4 (16.0)	3 (13.0)	0.553

oCR, overall complete response; cCR, complete clinical response; pCR, pathological complete response

[a] 23 out of 40 patients underwent surgery in the pTNT group

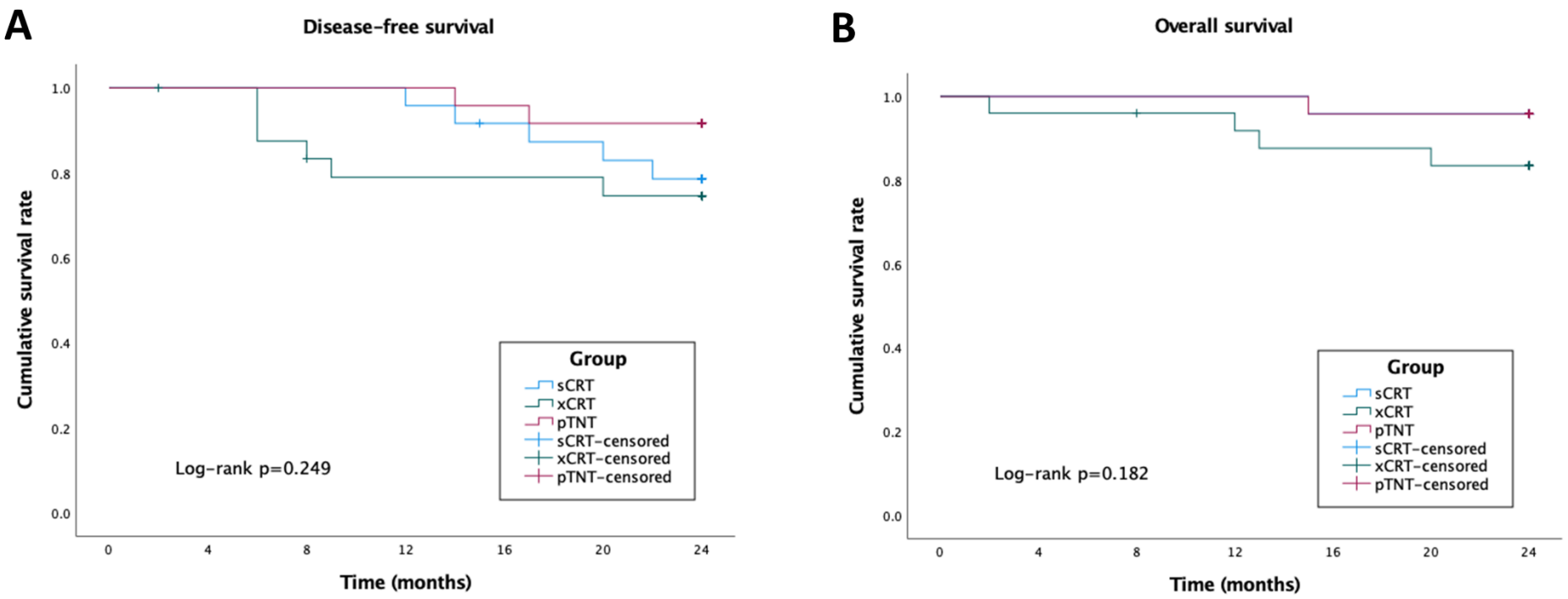

Figure. 33 Kaplan-Meier estimates of (A) disease-free survival and (B) overall survival in different study groups.

11.4.3 Surgical and pathological outcomes

Overall, 23 (57.5%) of 40 patients in the pTNT group, 25 (100%) in the xCRT group and 24 (100%) patients in the sCRT group proceeded to surgery (Table 31). The remaining 17 (42.5%) patients in the pTNT group have so far preserved their rectum. The median (range) interval between completion of radiotherapy and surgery was significantly longer in the pTNT group compared with xCRT and sCRT groups (172 days [76-616] vs 114 days [100-140] vs 112 days [98-134], P<0.001). No differences were noted in operative time (P=0.249), type of surgical approach (P=0.080) or type of resection (P=0.173). The proportion of patients with complete (R0) resection was high (91.7-95.7%) and similar across the three groups. There were no significant differences in the rate of anastomotic leak, 30-day postoperative complications according to the CD classification and length of hospital stay. There was no mortality within 30-day postoperative period. The quality of mesorectal resection was significantly higher in the pTNT group compared to xCRT and sCRT groups (91.3% vs 60% vs 58.3, P=0.049). There was no significant difference between the groups with respect to pathological T or N stage and TRG.

Table 31 Surgical and pathological outcomes				
	sCRT **N= 24**	**xCRT** **N=25**	**pTNT** **N=23**	**P-value**
Days from completion of radiotherapy to surgery	112 (98-134)	114 (100-140)	172 (76-616)	**<0.001**
Operative time, mins	274 (191-393)	246 (180-400)	246 (112-540)	0.249
Type of surgical approach				0.080
Laparoscopic	8 (33.3)	4 (16.0)	11 (47.8)	
Laparoscopic converted	2 (8.3)	1 (4.0)	0 (0.0)	
Open	14 (58.3)	20 (80.0)	12 (52.2)	
Type of resection[†]				0.173
Restorative	12 (50.0)	18 (72.0)	11 (47.8)	
Non-restorative	12 (50.0)	7 (28.0)	12 (52.2)	
Anastomotic leak[‡]	1 (8.3)	0 (0.0)	0 (0.0)	0.363
30-day postoperative complications (Clavien-Dindo grade)				0.675
None	14 (58.3)	12 (48.0)	14 (60.9)	
1 and 2	6 (25.0)	7 (28.0)	8 (34.8)	
3	3 (12.5)	5 (20.0)	1 (4.3)	
4	1 (4.2)	1 (4.0)	0 (0.0)	
Length of stay	8 (4-42)	9 (5-39)	7 (4-27)	0.295
Mesorectal grade				**0.049**
1	2 (8.3)	3 (12.0)	1 (4.3)	
2	8 (33.3)	7 (28.0)	1 (4.3)	
3	14 (58.3)	15 (60.0)	21 (91.3)	
Resection status				1.000
R0> 1mm	22 (91.7)	23 (92.0)	22 (95.7)	
R1≤ 1mm	2 (8.3)	2 (8.0)	1 (4.3)	
ypT stage				0.985

ypT0	6 (25.0)	5 (20.0)	3 (13.0)	
ypT1	2 (8.3)	1 (4.0)	1 (4.3)	
ypT2	4 (16.7)	5 (20.0)	6 (26.1)	
ypT3	11 (45.8)	13 (52.0)	12 (52.2)	
ypT4	1 (4.2)	1 (4.0)	1 (4.3)	
ypN stage				0.207
ypN0	19 (79.2)	16 (64.0)	20 (87.0)	
ypN1	2 (8.3)	5 (20.0)	3 (13.0)	
ypN2	3 (12.5)	4 (16.0)	0 (0.0)	
TRG				0.874
0	6 (25.0)	4 (16.0)	3 (13.0)	
1	10 (41.7)	11 (44.0)	8 (34.8)	
2	5 (20.8)	5 (20.0)	7 (30.4)	
3	3 (12.5)	5 (20.0)	5 (21.7)	

TRG, tumour regression grade

[a] Restorative procedures consisted of ultra-low or low anterior resections and non-restorative procedures consisted of abdominoperineal resections, Hartmann's, proctocolectomies and pelvic exenterations.

[b] Anastomotic leak was calculated including only patients with an anastomosis in the denominator.

11.5 Discussion

In this study, we found patients with LARC receiving pTNT have a significantly higher rate of oCR compared with those receiving xCRT or sCRT, but no significant difference in DFS and OS. Additionally, in the pTNT group, the cCR rate was approximately double that in the xCRT or sCRT groups, increasing the opportunity for NOM in patients seeking organ preservation. To our knowledge, this is the first multicentred study to compare treatment responses rates in patients with LARC treated with pTNT, xCRT or sCRT.

Previous studies by Habr-Gama et al. and Garcia-Aguilar et al. showed that sCRT followed by 2-3 cycles of consolidation chemotherapy has the potential to increase in pCR without severe adverse side effects compared to sCRT in patients with LARC.[408,409] Consequently, the WAIT randomised trial proceeded to test this hypothesis and found xCRT does not improve the pCR rate in patients with LARC. The authors of the WAIT trial however, acknowledged that the trial was underpowered to detect small differences in pCR between groups. Furthermore, Garcia-Aguilar et al. conducted the TIMING trial and reported a stepwise increase in pCR rates from 25% to 38% with the addition of more chemotherapy cycles.[126] This finding is also consistent with the results of the present study, that demonstrated a higher CR rate in patients who were administered an increased number of chemotherapy cycles and experienced a longer time interval between completion of radiotherapy and surgery (sCRT 112 vs xCRT 114 vs pTNT 172 days). The CAO/ARO/AIO-12 trial, which randomised patients to either induction or consolidation chemotherapy in the form of 3 cycles of FOLFOX before or after oxaliplatin based CRT followed by TME, demonstrated a much lower CR rate when compared with the current study (28% vs 52.5%).[410] Given these results, dose escalation in the form of 6 or more neoadjuvant chemotherapy cycles, and beyond the wait period interval, are expected to increase the CR rate.

Recent evidence suggests that TNT improves the pCR rate and may contribute to better disease-free survival for patients with LARC. Cercek et al. observed higher oCR rates and successful NOM with induction chemotherapy followed by CRT in comparison to sCRT.[387] The recently released results of the RAPIDO trial compared neoadjuvant short-course radiotherapy followed by 6 cycles of consolidation CAPOX or 9 cycles of FOLFOX4 followed by TME to sCRT, achieving a pCR rate of 28% and a significant reduction in the probability of distant metastasis in the TNT arm.[130] Additionally, the PRODIGE23 study comparing induction mFOLFIRINOX before CRT and TME followed by adjuvant chemotherapy to sCRT, also achieving a pCR rate of 28% and a significant improvement in DFS.[345] Further, there was no difference in surgical morbidity or compliance of CRT following induction chemotherapy.[345] In our study, no significant improvements were recorded in 2-year DFS or 2-year OS rates between the treatment groups. We attribute this result to the limited number of patients in each group and the short follow-up period. In the recently published OPRA trial, patients with LARC were randomised to receive induction or consolidation chemotherapy in the form of FOLFOX or CAPOX, followed by NOM for patients with cCR or near cCR.[42] Organ preservation at 3-years was achieved in 53% of the patients treated with consolidation TNT without compromising DFS when compared with sCRT. The pTNT group examined in the current study is a closer representation of both arms of the OPRA trial than previous RCTs assessing TNT. The baseline demographics of both studies were similar with clinical tumour and nodal staging together with treatment methodology in terms of chemotherapy agents and dosing and amount of chemoradiotherapy administered. These similarities may explain the similar cCR rates (47.5% vs 42.2%) between the OPRA trial and the present data. Whether a risk-adapted treatment strategy based on clinical staging at presentation (induction for distant failure risk and consolidation for local control), or a one size fits all approach (either induction or consolidation for everyone) is better remains to be clarified with data on this question still pending.

It is noteworthy that diagnostic criteria for cCR differed between the patient group undergoing pTNT and those in the WAIT trial. Strict criteria currently define cCR, and this mandates formation provided by three assessment modalities: clinical examination, endoscopic, and MRI.[411] However, radiological confirmation of cCR after CRT was not required during the WAIT trial, since surgery was mandated regardless of response. Therefore, although some patients in the WAIT trial were macroscopically diagnosed as having had cCR, for a subset of these patients, clinically undetectable residual tumour could have been present at the time of restaging. Thus, we speculate that the cCR rate may have been overestimated in the WAIT trial and suggest that the difference in response with pTNT could have been even more pronounced.

The current study has several other limitations. The small sample size which was limited through matching current prospective data (pTNT) to that of the WAIT Trial. Secondly, the period of time expired from completion of the WAIT trial to the adoption of pTNT may have introduced confounding bias, although other aspects of clinical care for LARC have not altered much in that time. Additionally, a common concern of TNT is acute toxicity to chemotherapy. While prospective toxicity data for the pTNT patients are available, they were not recorded as part of the WAIT trial, making comparisons difficult.[131] Lastly, variations in tumour response between the groups could be attributed to differences in treatment plans, patient characteristics and time intervals from completion of radiotherapy to surgery.

11.6 Conclusion

Compared with sCRT and xCRT, pTNT results in a significantly higher complete response rate which may facilitate organ preservation. No difference was noted in the 2-year DFS rates or 2-year OS rates between the three treatment groups. Long-term follow-up is required to determine whether pTNT impacts DFS or OS outcomes.

SYNOPSIS

This thesis provides novel insights into the following three questions:

1. Can a deep learning AI model be used to predict LN status on preoperative staging CT in patients with colon cancer?
2. Are clinical and biochemical factors, including sarcopenia, predictive of local response following neoadjuvant therapy in patients with LARC?
3. Is it feasible to tailor the sequencing of TNT according to clinical stage at presentation rather than applying a single standard regimen for all patients with advanced rectal cancer?

In the introduction, a brief overview of the incidence and mortality associated with CRC is discussed. The lymphatic metastatic pathway and relevant radiological imaging modalities are discussed primarily focusing on the challenge of accurately staging LNs and the implications for neoadjuvant and adjuvant therapy with their associated costs. Following this, a detailed section is presented on AI and how it can potentially improve the current method of staging LNs on preoperative imaging. The introduction then shifts towards clinical and biochemical predictors of local response to nCRT. The lack of accurate and reliable predictors is an issue that continues to court controversy and debate among surgeons and oncologists. Additionally, the introduction reviews the role of sarcopenia specifically, focusing on aetiology, diagnosis, association with negative oncological and postoperative outcomes in patients with CRC. In patients with LARC who undergo nCRT, distant metastasis rates have remained recalcitrant, owing to poor compliance to adjuvant chemotherapy. Accordingly, the last section of the introduction describes TNT, outlining the latest clinical trials and what questions still need to be answered.

The relevant questions are interrogated further in body of the thesis. **Chapter 3** systematically reviewed and meta-analysed the current AI methods in LN prediction on preoperative staging CT and MRI in patients with abdominopelvic malignancies. A total of 21 studies were included, 17 of whom were eligible for meta-analysis. This study highlighted the lack of deep learning studies (n=1) with the majority employing radiomics models (n=20). Heterogeneity and substantial risk of

bias were also noted in most studies. While radiomics models improve diagnostic accuracy of LN staging for abdominopelvic malignancies in comparison with radiologists, there remains insufficient data available on the accuracy of deep learning models for conducting a meta-analysis.

Chapter 4 focused on AI for pre-operative lymph node staging in colorectal cancer. A second systematic review and meta-analysis was performed. Seventeen studies were included, of which twelve used radiomics and five employed deep learning. In rectal cancer the accuracy of a deep learning model in a per-patient lymphadenopathy diagnosis was higher than radiomics, and both models performed better than radiologists. There was significant heterogeneity between studies. Data on the diagnostic accuracy of deep learning models in CRC remain scarce, thus limiting our ability to perform a meta-analysis. Overall, this study showed a potential role for deep learning models to be used as a diagnostic tool for staging lymph nodes on preoperative imaging, however, higher quality studies with larger sample sizes are required.

Chapter 5 established the baseline accuracy of nodal staging in colon cancer and tumour and nodal staging in rectal cancer at our institutions. We prospectively evaluate the diagnostic agreement between MDT review and radiology reports. Of 346 eligible patients with colon cancer, 270 patients had available histopathology which served as the ground truth to measure diagnostic accuracy. This study showed no significant differences in local CRC staging between MDT review and original radiology reports. It further shows that the accuracy of preoperative nodal staging was 70% in patients with colon cancer which is in line with the nodal accuracy observed historically. Moreover, the results of this study served as a baseline accuracy of the radiologist assessment of LNs that could later be compared to the accuracy of the deep learning model.

Chapter 6 describes an original study to develop a deep learning model to identify nodal disease based on preoperative staging CT using larger numbers of patients and with more robust

methodology than in the literature identified in the reviews. A ResNet-50 framework was used that integrates a segmentation model with a classification model. The combination of the two models allowed to transfer the learned features from segmentations across to the classifier. Of a total of 1201 patients, 401 were allocated to the training, 100 to validation, 500 to retrospective testing and 200 to prospective testing. On prospective testing the ResNet-50 deep learning model predicted the presence or absence of metastatic disease in local lymph nodes poorly with an AUROC of 0.486. Ultimately, we show that a ResNet-50 framework is unable to accurately stage lymph nodes on preoperative CT imaging in patients with colon cancer.

Despite rigorous modelling and a large sample size, the deep learning model developed in **Chapter 6** had limited accuracy and a low AUROC thereby suggesting that the deep learning model did not predict lymph node status. Consequently, we shifted towards another existing area in need of more research which is the role of AI for body composition and sarcopenia evaluation on CT. **Chapter 7** was a systematic review and meta-analysis conducted to summarise the available CT- based AI segmentation models able to determine body composition and to assess the performance of these models. Twenty-four studies were systematically reviewed, of those 15 studies were meta-analysed. CT-based deep learning segmentation models demonstrated excellent performance in body composition and sarcopenia measurement. Although more comparative data is needed before incorporating these models into clinical practice, it is unnecessary to develop new deep learning segmentation models given the available models demonstrated over 90% overlap between the prediction output and the ground truth.

The second part of this thesis focusses on predictors of response to neoadjuvant treatment. **Chapter 8** investigated if sarcopenia could predict local response after nCRT in patients with LARC. Pre-treatment sarcopenia was diagnosed using total psoas index calculated from staging CT scans. The primary outcome used was pathological tumour regression grade defined as good (tumour

regression grade 0/1) versus poor (tumour regression grade 2/3). Secondary outcomes were pCR and assumed CR (cCR + pCR). Of 167 included patients with LARC, 157 proceeded to surgery. There was no significant difference between good tumour regression grade, pCR and assumed CR patients in the sarcopenia group compared with the non-sarcopenia group. This study showed that sarcopenia is not a predictor of poor nCRT response in patients with LARC. Further multicentre studies are required to explore the mechanism of the relationship between sarcopenia and pCR to nCRT. In **Chapter 9** we explored clinical and biochemical predictors of local response after neoadjuvant therapy in patients with rectal cancer. The primary outcomes were tumour regression grade based on radiological imaging (mrTRG) or pathology (pTRG). Patients were classified as good (mrTRG 1-2 or pTRG 0-1) versus poor TRG (mrTRG 3-4 or pTRG 2-3). Out of 274 included patients with rectal cancer, 228 proceeded to surgery. On regression analysis clinical T2 stage and BMI≥25kg/m^2 were significant predictors of a good TRG and clinical T2 stage and a pTNT regimen were predictors of achieving a CR. The diagnostic AUC for the regression models were 0.63 for good TRG and 0.62 for achieving a CR. Together, these findings suggest that a clinical T2 stage and BMI≥25kg/m^2 were predictors of good response to neoadjuvant therapy in patients with rectal cancer. After external validation, this information can potentially improve standard of care by more accurately stratifying patients to neoadjuvant therapy and help patients improve their outcome.

In the third part of this thesis, the role of personalised sequencing of TNT was interrogated. **Chapter 10** presents a prospective evaluation short term outcomes of a personalised Total Neoadjuvant Treatment (pTNT) protocol, with treatment sequencing based on clinical stage at presentation. Of 270 patients referred with rectal cancer, 102 received pTNT with curative intent and 79 have completed their treatment thus far. Thirty-three patients (41.8%) received induction chemotherapy and 46 (58.2%) received consolidation chemotherapy per protocol. Overall, a cCR was observed in 40.5% of patients and organ preservation was possible in 35.2% of patients treated

with pTNT. Of the 29 patients with distant disease, a complete M1 response was observed in 44.8% of patients. Preliminary results suggest pTNT may provide the optimal balance between local and distant disease control and treatment toxicity for patients with advanced rectal cancer. Long-term data to examine recurrence and survival rates are required and pending.

Lastly, in **Chapter 11** we compared treatment response rates with pTNT versus chemotherapy in the 'wait period' (xCRT) or standard Chemoradiotherapy (sCRT). Prospective data of all patients with rectal cancer considered for pTNT over a 3.9-year period was matched to a historical cohort of patients treated with xCRT or sCRT. We found that oCR was significantly higher in patients treated with pTNT which consisted of 8 cycles mFOLFOX6 or 6 cycles CAPOX without adjuvant therapy than in those treated with either 3 cycles 5-FU/LV during the 10-week wait period after chemoradiotherapy or standard chemoradiotherapy, followed by adjuvant chemotherapy. We found no significant difference in 2-year DFS rates or 2-year OS rates between the three treatment groups.

CONCLUSIONS

Based on the collective research presented in this thesis, a few conclusions can be drawn.

Firstly, there is a considerable heterogeneity among studies using AI for LN staging on preoperative MRI and CT in CRC. There is also a lack of studies using deep learning to predict LN stage on preoperative CT imaging, specifically in colon cancer. In the only study published to date, and with the inclusion of a large number of patients and a robust model, we were unable to demonstrate that a deep learning model using a ResNet-50 framework can accurately stage lymph nodes in patients with colon cancer.

We therefore pivoted to examine which markers can be correlated with tumour response to nCRT. We identified clinical T2 stage and a BMI≥25kg/m^2, are significant predictors of a good TRG response after neoadjuvant therapy in patients with rectal cancer, but that sarcopenia was not predictive.

Thirdly, we showed that a defined two schema pTNT protocol tailoring treatment sequencing to disease risk at presentation may represent optimal balance between local and distant disease control. We also found that compared with sCRT and xCRT, pTNT results in a significantly higher complete response rate which may facilitate organ preservation.

FUTURE DIRECTIONS

The first part of this thesis has outlined the current evidence in the diagnostic accuracy of AI models in predicting LN status on preoperative imaging in abdominopelvic malignancies and CRC and has established a baseline rate that can be achieved by the radiologist. While the ResNet-50 deep learning model was unable to accurately stage LNs on preoperative CT imaging in colon cancer, radiomics is the logical next step in uncovering the distinguishing features between malignant and benign LNs. Creating a reliable radiomics model that can accurately stage regional LNs in patients with CRC could potentially give clinicians the ability to more accurately tailor patient's treatment, maximise tumour response, reduce chemotherapy dosage or avoid unnecessary treatment and improve overall outcome and quality of life.

The second part of this thesis has shown that in patients with LARC, sarcopenia does not predict local response after nCRT, however clinical T2 stage and a BMI≥25kg/m^2 were shown to be predictors of good response. Nevertheless, the diagnostic accuracy of the multivariable regression model based on the predictors of good TRG was not high enough to be implemented in the clinical setting. A larger multicentre prospective study conducted with a factorial, pragmatic design could add power and external validation of the results.

The third part of this thesis has demonstrated increased rates of cCR and CR with a pTNT protocol in patients with advanced rectal cancer. Recently, Cercek et al. conducted a phase II study investigating Programmed Death (PD1) blockade in mismatch repair-deficient LARC.[412] Results of their study showed a cCR in 100% of patients. Although a phase III study is required to confirm the success of immunotherapy in this subpopulation of LARC, the future of TNT lies in exploring novel therapies that target individual mutations in genetic sequencing pathways including KRAS/NRAS, BRAF, HER amplification and gene fusion. Adding new more targeted therapeutic agents to an existing pTNT platform may further improve response rates and reduce toxicity.

APPENDIX – A: SUPPEMENTARY MATERIAL FOR ARTIFICIAL INTELLIGENCE FOR THE DIAGNOSIS OF LYMPH NODE METASTASES IN PATIENTS WITH ABDOMINOPELVIC MALIGNANCY: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Appendix 1. Prisma checklist[150]

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9,10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11,12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15,16,17
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	23,24,25
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	20,21
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16,17,18,19
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	22
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	26
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	28
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	30

APPENDIX – B: SUPPEMENTARY MATERIAL FOR ARTIFICIAL INTELLIGENCE FOR PRE-OPERATIVE LYMPH NODE STAGING IN COLORECTAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Table 1. Search Strategy

Sources	Search in	MeSH terms	Limits	Search results
Cochrane Library	Search manager	("Artificial intelligence" OR "deep learning" OR "convolutional neural network" OR "machine learning" OR "automatic detection" OR "radiomics" OR "radiomic") AND ("CT" OR "MRI") AND ("Lymph node" OR "lymph node metastasis") AND ("colon" OR "rectal" OR "colorectal")	None	3
PubMed, (MEDLINE)	N/A	("Artificial intelligence" OR "deep learning" OR "convolutional neural network" OR "machine learning" OR "automatic detection" OR "radiomics" OR "radiomic") AND ("CT" OR "MRI") AND ("Lymph node" OR "lymph node metastasis") AND ("colon" OR "rectal" OR "colorectal")	Research articles, years (2010-2020)	14
EMBASE	Quick search	('artificial intelligence'/exp OR 'artificial intelligence' OR 'deep learning'/exp OR 'deep learning' OR 'convolutional neural network'/exp OR 'convolutional neural network' OR 'machine learning'/exp OR 'machine learning' OR 'automatic detection' OR 'radiomics'/exp OR 'radiomics' OR 'radiomic') AND ('ct'/exp OR 'ct' OR 'mri'/exp OR 'mri') AND ('lymph node'/exp OR 'lymph node' OR 'lymph node metastasis'/exp OR 'lymph node metastasis') AND ('colon'/exp OR 'colon' OR 'rectal' OR 'colorectal')	None	45
IEEE Xplore Digital Library	N/A	(“Artificial intelligence” OR “machine learning” OR “deep learning” OR “convolutional neural network” OR “automatic detection” OR “computer-aided” OR “segmentation” OR “Radiomic” OR “Radiomics”) AND (“CT” OR “MRI” OR “images” OR “diagnostic imaging” OR “radiology”) AND (“Lymph node*” OR “lymph node detection”)	None	3

Table 2. Diagnostic accuracy measures

Measure	Formula
Sensitivity	$\frac{TP}{P} = \frac{TP}{TP + FN}$
Specificity	$\frac{TN}{N} = \frac{TN}{TN + FP}$
Accuracy	$\frac{TP + TN}{P + N} = \frac{TP + TN}{TP + TN + FP + FN}$
PPV	$\frac{TP}{TP + FP}$
NPV	$\frac{TN}{TN + FN}$
SE	$\frac{(Upper\ Limit - Lower\ Limit)}{3.92}$
95% Confidence Interval	$best\ estimate +/- (1.96) * (SE)$

Table 3. Selected characteristics of included studies.										
First Author	**Country**	**Year**	**Study design**	**Patients (% female patients)**	**Sample size for diagnostic accuracy, n**	**Mean or Median age (SD; range), years***	**Imaging modality**	**Type of malignancy**	**AI model (Per-patient /per-node diagnostic output)**	**Reference standard**
Ding [186]	China	2020	Prospective single-center	545 (38%)	183	58.6 (12.6)	MRI	Rectal	Deep learning (per-patient)	Pathology
Eresen[193]	USA	2020	Retrospective single-center	390 (47%)	78	62.1 (±13.25) LN (+), 62.56 (±14.17) LN (-)	CT	Colon	Radiomics (per-patient)	Pathology
Li[194]	China	2020	Prospective single-center	766 (45%)	308	59.0 (±12.03;19-87)	CT	Colorectal	Radiomics (per-patient)	Pathology
Yang[195]	China	2020	Retrospective single-center	139 (35%)	41	64 (34-86)	MRI	Rectal	Radiomics (per-patient)	Pathology
Nakanishi[196]	Japan	2020	Retrospective Multi-center	247 (34%)	72	61 (51.3–72.8)	CT	Rectal	Radiomics (per-patient)	Pathology
Zhou[197]	China	2020	Retrospective Single-center	391 (29%)	130	53.7 ± 11.7	MRI	Rectal	Radiomics (per-patient)	Pathology
Glaser[47]	Australia	2020	Retrospective Single-center	123	23	-	CT	Colon	Deep learning (per-patient)	Pathology
Meng [198]	China	2019	Retrospective Single-center	345 (38%)	148	61.1 (±12.4)	MRI	Rectal	Radiomics (per-patient)	Pathology
Wang[185]	China	2019	Retrospective single-center	107	-	-	CT	Rectal	Deep learning (per-patient)	-

Zhu[199]	China	2019	Retrospective Single-center	215 (39%)	72	58.6 (±10.3)	MRI	Rectal	Radiomics (per-node)	Pathology
Lu[200]	China	2018	Prospective multi-center	765	414	-	MRI	Rectal	Deep learning (per-node)	Pathology
Li[201]	China	2018	Retrospective single center	619	-	-	MRI	Colorectal	Deep learning (per-node)	Radiology
Chen[202]	China	2018	Prospective Single-center	115 (43%)	33	57 (± 14;30–79) LN (+), 62 (± 14;29–85)	ERUS, CT, SWE	Rectal	Radiomics (per-patient)	Pathology
Huang[203]	China	2016	Retrospective Single-center	326 (35%)	200	61.2 (±13.9), 60.0 (±13.5) LN (+), 64.9 (±11.8) LN (-)	CT	Colorectal	Radiomics (per-patient)	Pathology
Cai[157]	China	2012	Prospective Single-center	228 (39%)	Avg of leave-one-out CV	58 (19-86)	CT	Rectal	Radiomics (per-node)	Pathology
Tse[205]	UK	2012	Retrospective Multi-center	17	Avg of leave-one-out CV	-	MRI	Rectal	Radiomics (per-node)	Pathology
Cui[204]	China	2011	Prospective Single-center	228	Avg of leave-one-out CV	-	CT	Rectal	Radiomics (per-node)	Pathology

AI, artificial intelligence; Avg, average; CV, cross validation

Table 4. Quality assessment of studies included in systematic review, according to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) Tool adapted with signalling questions by Sollini et al.

(Sollini M, Antunovic L, Chiti A, Kirienko M: Towards clinical application of image mining: a systematic review on artificial intelligence and radiomics. Eur J Nucl Med Mol Imaging 2019, 46(13):2656-2672.)

Source	RISK OF BIAS								APPLICABILITY CONCERNS		
	PATIENT SELECTION			INDEX TEST			REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
	Was the statistical management adequate?	Were the inclusion /exclusion criteria specified?	Was the type of study (retrospective or prospective) specified?	Were the imaging acquisition protocol and the segmentation method(s) detailed?	Was the image processing approach detailed?	Was the validation independent (i.e., no internal)?	Was the reference standard adequate?	Was there an appropriate interval between index test and reference standard?			
Ding et al 2020 [186]	yes	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes
Eresen et al 2020 [193]	yes	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes
Li et al 2020 [194]	yes	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes

Yang et al 2020 [195]	yes	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes
Nakanishi et al 2020[196]	yes	yes	yes	yes	yes	yes	yes	unclear	yes	yes	yes
Zhou et al 2020 [197]	yes	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes
Glaser et al 2020 [47]	yes	no	yes	yes	yes	no	yes	unclear	yes	yes	yes
Meng et al 2019 [198]	yes	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes
Wang et al 2019 [185]	yes	no	yes	yes	no	no	unclear	unclear	yes	yes	unclear
Zhu et al 2019 [199]	yes	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes
Lu et al 2018 [200]	yes	yes	yes	yes	yes	yes	yes	unclear	yes	yes	yes
Li et al 2018 [201]	yes	yes	yes	yes	yes	no	no	unclear	yes	yes	yes
Chen et al 2018[202]	yes	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes
Huang et al 2016 [203]	yes	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes
Cai et al 2012 [157]	yes	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes
Tse et al 2012 [205]	yes	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes
Cui et al 2011 [204]	yes	yes	yes	yes	yes	no	yes	unclear	yes	yes	yes

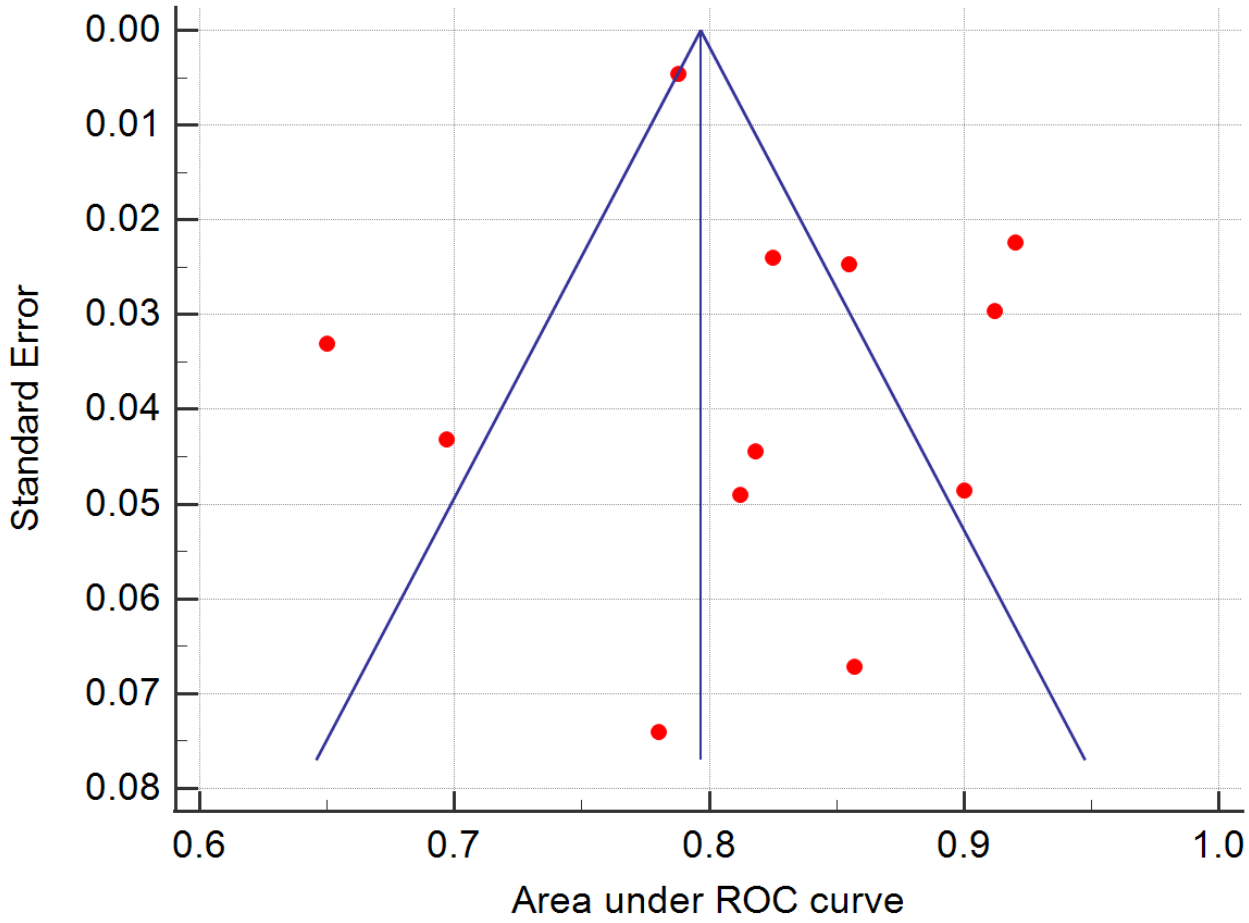

Figure. 1 Publication bias presentation using funnel plot of included studies.

APPENDIX – C: SUPPEMENTARY MATERIAL FOR DEEP LEARNING TO PREDICT LYMPH NODE STATUS ON PRE-OPERATIVE STAGING CT IN PATIENTS WITH COLON CANCER.

Table 1. Scanner types		
Manufacturer	**Type**	**Year**
Philips	Brilliance 16-Slice	2007-2009
Toshiba	Aquilion 32	2011
GE	LightSpeed VCT	2007-2019
GE	Optima	2012-2019
Siemens	SOMATOM Single and Dual Source series	2007-2019
Philips	5000 Ingenuity	2011-2019
Siemens	SOMATOM Definition AS	2019
Toshiba	Aquilion ONE	2019
Siemens	SOMATOM Force	2019
Siemens	SOMATOM 256	2012-2019
Siemens	SOMATOM Perspective	2019

Table 2. CT scan characteristics					
Variables	**Training Cohort (n=401)**	**Validation Cohort (n=100)**	**Testing Cohort 1 (n=500)**	**Testing Cohort 2 (n=200)**	**P-value**
LN segmentation	401 (100.0)	100 (100.0)	n/a	n/a	n/a
Contrast-enhanced CT					0.361
Yes	373 (93.0)	91 (91.0)	475 (95.0)	189 (94.5)	
No	28 (7.0)	9 (9.0)	25 (5.0)	11 (5.5)	
CT scan slice thickness					<0.001
0.5 mm	5 (1.2)	2 (2.0)	5 (1.0)	3 (1.5)	
1 mm	38 (9.5)	12 (12.0)	19 (3.8)	65 (32.5)	
1.25 mm	51 (12.7)	5 (5.0)	33 (6.6)	1 (0.5)	
1.5mm	3 (0.7)	3 (3.0)	3 (0.6)	0 (0.0)	
2 mm	105 (26.2)	41 (41.0)	30 (6.0)	1 (0.5)	
2.5 mm	50 (12.5)	8 (8.0)	47 (9.4)	18 (9.0)	
3 mm	118 (29.4)	24 (24.0)	282 (56.4)	109 (54.5)	
5 mm	26 (6.5)	4 (4.0)	78 (15.6)	3 (1.5)	
7 mm	5 (1.2)	1 (1.0)	3 (0.6)	0 (0.0)	

CT, computed tomography; LN, lymph node; n/a, not applicable

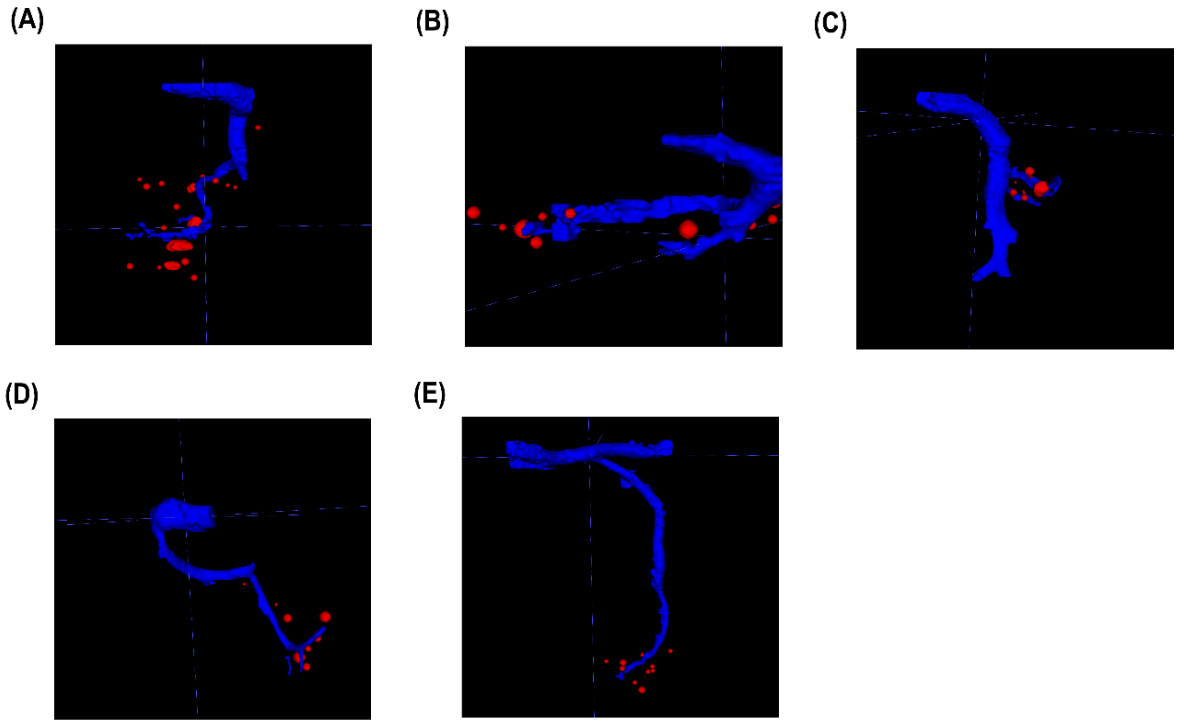

Figure. 1 Regional lymph nodes are segmented in red around the colonic veins segmented in blue (colonic veins are segmented for illustrative purposes only). (A) Ileocolic nodes. (B) Right colic nodes. (C) Middle colic nodes. (D) Left colic nodes. (E) Sigmoid nodes.

APPENDIX – D: SUPPEMENTARY MATERIAL FOR ARTIFICIAL INTELLIGENCE FOR BODY COMPOSITION AND SARCOPENIA EVALUATION ON COMPUTED TOMOGRAPHY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Table 1. Search Strategy				
Sources	Search in	MeSH terms	Limit	Results
PubMed, (MEDLINE)	N/A	(“Artificial intelligence” OR “deep learning” OR “convolutional neural network” OR “machine learning” OR “automatic detection” OR “vector machine” OR "radiomics" OR "radiomic") AND (“CT” OR “computed tomography”) AND (“age-related sarcopenia” OR “body composition” OR “dynapenia” OR “myopenia” OR “sarcopenic obesity” OR “sarcopenia”)	10yrs	56
EMBASE	Quick search	(“Artificial intelligence” OR “deep learning” OR “convolutional neural network” OR “machine learning” OR “automatic detection” OR “vector machine” OR "radiomics" OR "radiomic") AND (“CT” OR “computed tomography”) AND (“age-related sarcopenia” OR “body composition” OR “dynapenia” OR “myopenia” OR “sarcopenic obesity” OR “sarcopenia”)	None	104
Web of Science	Basic search	(“Artificial intelligence” OR “deep learning” OR “convolutional neural network” OR “machine learning” OR “automatic detection” OR “vector machine” OR "radiomics" OR "radiomic") AND (“CT” OR “computed tomography”) AND (“age-related sarcopenia” OR “body composition” OR “dynapenia” OR “myopenia” OR “sarcopenic obesity” OR “sarcopenia”)	10yrs	55
Scorpus	Abstract title, Abstract, keywords	TITLE-ABS-KEY ((“Artificial intelligence” OR “deep learning” OR “convolutional neural network” OR “machine learning” OR “automatic detection" OR “vector AND machine” OR "radiomics" OR "radiomic") AND (" CT" OR "computed tomography") AND ("sarcopenia" OR “body AND composition”))	None	24

Table 2. Checklist for Artificial Intelligence in Medical Imaging (CLAIM)		
Section / Topic	No.	Item
TITLE / ABSTRACT		
	1	Identification as a study of AI methodology, specifying the category of technology used (e.g., deep learning)
	2	Structured summary of study design, methods, results, and conclusions
INTRODUCTION		
	3	Scientific and clinical background, including the intended use and clinical role of the AI approach
	4	Study objectives and hypotheses
METHODS		
Study Design	**5**	Prospective or retrospective study
	6	Study goal, such as model creation, exploratory study, feasibility study, non-inferiority trial
Data	**7**	Data sources
	8	Eligibility criteria: how, where, and when potentially eligible participants or studies were identified (e.g., symptoms, results from previous tests, inclusion in registry, patient-care setting, location, dates)
	9	Data pre-processing steps
	10	Selection of data subsets, if applicable
	11	Definitions of data elements, with references to Common Data Elements
	12	De-identification methods
	13	How missing data were handled
Ground Truth	**14**	Definition of ground truth reference standard, in sufficient detail to allow replication
	15	Rationale for choosing the reference standard (if alternatives exist)
	16	Source of ground-truth annotations; qualifications and preparation of annotators
	17	Annotation tools
	18	Measurement of inter- and intrarater variability; methods to mitigate variability and/or resolve discrepancies
Data Partitions	**19**	Intended sample size and how it was determined
	20	How data were assigned to partitions; specify proportions
	21	Level at which partitions are disjoint (e.g., image, study, patient, institution)

Model	**22**	Detailed description of model, including inputs, outputs, all intermediate layers and connections
	23	Software libraries, frameworks, and packages
	24	Initialization of model parameters (e.g., randomization, transfer learning)
Training	**25**	Details of training approach, including data augmentation, hyperparameters, number of models trained
	26	Method of selecting the final model
	27	Ensembling techniques, if applicable
Evaluation	**28**	Metrics of model performance
	29	Statistical measures of significance and uncertainty (e.g., confidence intervals)
	30	Robustness or sensitivity analysis
	31	Methods for explainability or interpretability (e.g., saliency maps), and how they were validated
	32	Validation or testing on external data
RESULTS		
Data	**33**	Flow of participants or cases, using a diagram to indicate inclusion and exclusion
	34	Demographic and clinical characteristics of cases in each partition
Model performance	**35**	Performance metrics for optimal model(s) on all data partitions
	36	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)
	37	Failure analysis of incorrectly classified cases
DISCUSSION		
	38	Study limitations, including potential bias, statistical uncertainty, and generalizability
	39	Implications for practice, including the intended use and/or clinical role
OTHER INFORMATION		
	40	Registration number and name of registry
	41	Where the full study protocol can be accessed
	42	Sources of funding and other support; role of funders

Table 3. CLAIM individual scoring per study per rater

Rater 1:

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Kroll et al., 2021[286]	1	1	1	1	1	0	1	1	1	0	1	0	0	1	1	1	0	0	0	1	1	1	0	1	1	0	n/a	0	1	0	0	0	0	1	1	0	0	1	1	1	0	1
Borrelli et al., 2021[287]	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	0	0	1	1	1	0	0	1	0	n/a	1	0	0	1	1	0	1	1	1	1	1	1	1	1	1
Amarasinghe et al., 2021[288]	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1
Ackermans et al., 2021[289]	1	1	1	1	0	1	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	n/a	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Magudia et al., 2021 [290]	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	n/a	1	1	1	1	1	0	0	1	1	1	1	1	1	0	1
Zopfs et al., 2020 [291]	1	1	1	1	1	1	1	1	1	1	1	0	n/a	1	1	1	1	1	0	1	1	1	1	1	1	0	n/a	1	0	0	1	0	0	1	1	1	1	1	1	1	0	1
Burns et al., 2020 [275]	1	1	1	1	1	1	1	1	1	n/a	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	n/a	0	1	0	1	0	1	1	1	0	0	1	1	1	0	1
Koitka et al., 2020 [292]	1	1	1	1	1	0	1	1	1	n/a	0	0	n/a	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	1	0	0	1	1	0	0	0
Park et al., 2020[293]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	n/a	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
Liu et al., 2020[294]	1	1	1	1	1	0	1	0	1	n/a	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	1	1	0	1	1	0	0	1
Paris et al., 2020[295]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	n/a	1	1	1	1	0	0	1	1	1	0	1	1	0	0	1
Hemke et al.,2020[296]	1	1	1	1	1	0	1	1	1	n/a	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	0	n/a	1	0	0	1	0	0	0	1	1	0	1	1	0	0	1
Blanc-Durand et al., 2020[297]	1	1	1	1	1	0	1	1	1	n/a	0	0	0	1	0	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	0	0	1
Nowak et al., 2020[298]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	1
Dong et al., 2019[299]	1	1	1	1	1	0	1	1	1	0	1	0	0	0	0	0	1	1	0	1	1	1	1	1	1	1	n/a	1	0	1	1	0	0	0	1	0	0	1	1	0	0	0
Graffy et al.,2019[300]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	0	0	0	1	1	1	1	1	1	n/a	1	1	1	1	0	0	1	1	1	1	1	1	0	0	0
Barnard et al.,2019[301]	1	1	1	1	1	0	1	1	1	0	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	n/a	1	1	0	1	0	0	0	1	1	0	1	1	0	0	1
Hashimoto et al.,2019[302]	1	0	1	1	0	1	1	0	0	1	1	0	0	1	0	1	1	0	0	1	1	1	1	1	1	1	n/a	1	0	0	1	1	0	0	1	0	1	1	1	0	0	0
Dabiri et al.,2019[278]	0	0	1	1	0	1	1	0	1	1	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	n/a	1	1	1	1	1	0	0	1	1	0	1	1	0	0	1
Weston et al., 2019[303]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	n/a	1	1	1	1	0	0	1	1	1	1	1	1	0	0	0
Liu et al., 2019[304]	1	0	1	1	0	0	0	1	1	1	1	0	0	1	0	1	1	0	0	1	1	1	1	1	1	1	n/a	1	1	0	1	0	0	0	1	1	0	1	1	0	0	0
Gonzalez et al. 2018[305]	0	0	0	1	1	0	1	0	0	0	1	0	n/a	1	0	1	1	0	0	1	0	1	0	1	1	1	1	1	1	0	1	0	0	0	1	1	0	0	0	0	0	1
Wang et al., 2017[306]	1	0	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	n/a	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1
Lee et al., 2017[307]	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	n/a	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0

Rater 2:

Kroll et al., 2021[286]	1	0	1	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	0	1	1	0	1	1	1	1	n/a	0	1	0	0	0	0	1	1	0	0	1	1	0	0	1

Borrelli et al., 2021[287]	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	0	1	1	1	1	1	0	1	1	n/a	1	0	0	1	0	0	1	1	1	0	1	1	1	0	1
Amarasinghe et al., 2021[288]	1	1	1	1	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	0	1	1	1	1	1	1	1
Ackermans et al., 2021[289]	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	n/a	1	0	0	1	1	1	1	1	1	0	1	1	1	1	1
Magudia et al., 2021 [290]	1	1	1	1	0	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	n/a	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
Zopfs et al., 2020 [291]	1	1	1	1	1	1	1	1	1	1	1	0	n/a	1	1	1	1	1	0	1	1	1	1	1	1	0	n/a	1	1	0	1	0	0	0	1	1	0	1	1	1	1	1
Burns et al., 2020 [275]	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	n/a	0	1	0	1	0	1	1	1	0	0	1	1	1	0	1
Koitka et al., 2020 [292]	1	1	1	1	1	1	1	1	1	0	0	0	n/a	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	1	1	0	1	0	0	0	1
Park et al., 2020[293]	1	1	1	1	1	1	0	1	1	1	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	n/a	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
Liu et al., 2020[294]	1	1	1	1	1	0	0	0	1	n/a	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	0	1	1	0	0	1
Paris et al., 2020[295]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	0	n/a	0	1	1	0	0	0	1	1	1	0	1	1	0	0	1
Hemke et al.,2020[296]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	n/a	1	0	0	0	0	0	0	1	1	0	1	1	0	0	1
Blanc-Durand et al., 2020[297]	1	1	1	1	1	0	1	1	1	n/a	0	0	0	1	1	0	1	0	0	1	1	1	0	1	1	0	1	1	1	0	1	1	0	0	1	1	0	1	1	0	0	1
Nowak et al., 2020[298]	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	1
Dong et al., 2019[299]	1	1	1	1	1	0	1	1	1	0	1	0	0	0	0	0	1	1	0	1	1	1	1	1	1	1	n/a	1	0	1	1	0	0	0	1	0	0	1	1	0	0	0
Graffy et al.,2019[300]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	0	0	0	1	1	1	1	1	1	n/a	1	1	1	1	0	0	1	1	1	1	1	1	0	0	0
Barnard et al.,2019[301]	1	1	1	1	1	0	1	1	1	0	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	n/a	1	0	0	1	0	0	0	1	1	0	1	1	0	0	1
Hashimoto et al.,2019[302]	1	0	1	1	0	1	1	0	0	1	1	0	0	1	0	1	1	0	0	1	1	1	1	1	1	1	n/a	1	0	0	1	1	0	0	1	0	1	1	1	0	0	0
Dabiri et al.,2019[278]	0	0	1	1	0	0	1	0	0	1	1	0	0	1	1	1	1	0	0	1	1	1	1	1	0	1	n/a	1	0	0	1	0	0	0	1	1	0	1	1	0	0	1
Weston et al., 2019[303]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	n/a	0	1	1	1	0	1	1	1	1	1	1	0	0	0	1
Liu et al., 2019[304]	1	0	1	1	1	0	1	0	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	n/a	1	1	0	1	0	0	0	1	1	0	1	1	0	0	0
Gonzalez et al. 2018[305]	1	1	1	1	1	1	1	0	1	1	1	0	1	1	0	0	1	1	1	1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1
Wang et al., 2017[306]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	1	1	1	0	1	n/a	1	1	1	1	1	1	1	0	1	0	1	1	0	0	1
Lee et al., 2017[307]	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	n/a	1	1	1	1	1	1	0	1	1	0	1	1	0	0	0
Rater 1 and Rater 2:																																										
Kroll et al., 2021[286]	1	1	1	1	1	0	1	1	1	0	1	0	0	1	1	1	0	0	0	1	1	1	0	1	1	0	n/a	0	1	0	0	0	0	1	1	0	0	1	1	0	0	1
Borrelli et al., 2021[287]	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	0	0	1	1	1	0	0	1	0	n/a	1	0	0	1	1	0	1	1	1	0	1	1	1	0	1
Amarasinghe et al., 2021[288]	1	1	1	1	1	1	1	1	0	0	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1
Ackermans et al., 2021[289]	1	1	1	1	0	1	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	n/a	1	0	0	1	1	1	1	1	1	0	1	1	1	1	1
Magudia et al., 2021 [290]	1	1	1	1	0	1	1	1	1	0	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	0	n/a	1	1	1	1	1	0	0	1	1	0	1	1	1	0	1

Zopfs et al., 2020 [291]	1	1	1	1	1	1	1	1	1	1	1	0	n/a	1	1	1	1	1	0	1	1	1	1	1	1	0	n/a	1	0	0	1	0	0	1	1	1	0	1	1	1	0	1
Burns et al., 2020 [275]	1	1	1	1	1	1	1	1	1	n/a	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	n/a	0	1	0	1	0	1	1	1	0	0	1	1	1	0	1
Koitka et al., 2020 [292]	1	1	1	1	1	0	1	1	1	n/a	0	0	n/a	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	1	0	0	0	1	0	0	1	1	0	0	1
Park et al., 2020[293]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	n/a	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
Liu et al., 2020[294]	1	1	1	1	1	0	1	0	1	n/a	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	1	1	0	1	1	0	0	1
Paris et al., 2020[295]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	0	n/a	1	1	1	1	0	0	1	1	1	0	1	1	0	0	1
Hemke et al.,2020[296]	1	1	1	1	1	0	1	1	1	n/a	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	0	n/a	1	0	0	1	0	0	0	1	1	0	1	1	0	0	1
Blanc-Durand et al., 2020[297]	1	1	1	1	1	0	1	1	1	n/a	0	0	0	1	0	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	0	1	1	0	0	1
Nowak et al., 2020[298]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	1
Dong et al., 2019[299]	1	1	1	1	1	0	1	1	1	0	1	0	0	0	0	0	1	1	0	1	1	1	1	1	1	1	n/a	1	0	1	1	0	0	0	1	0	0	1	1	0	0	0
Graffy et al.,2019[300]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	0	0	0	1	1	1	1	1	1	n/a	1	1	1	1	0	0	1	1	1	1	1	1	0	0	0
Barnard et al.,2019[301]	1	1	1	1	1	0	1	1	1	0	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	n/a	1	1	0	1	0	0	0	1	1	0	1	1	0	0	1
Hashimoto et al.,2019[302]	1	0	1	1	0	1	1	0	0	1	1	0	0	1	0	1	1	0	0	1	1	1	1	1	1	1	n/a	1	0	0	1	1	0	0	1	0	1	1	1	0	0	0
Dabiri et al.,2019[278]	0	0	1	1	0	1	1	0	1	1	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	n/a	1	1	1	1	1	0	0	1	1	0	1	1	0	0	1
Weston et al., 2019[303]	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1	n/a	1	1	1	1	0	0	1	1	1	1	1	1	0	0	0
Liu et al., 2019[304]	1	0	1	1	0	0	0	1	1	1	1	0	0	1	0	1	1	0	0	1	1	1	1	1	1	1	n/a	1	1	0	1	0	0	0	1	1	0	1	1	0	0	0
Gonzalez et al. 2018[305]	0	0	0	1	1	0	1	0	0	0	1	0	n/a	1	0	1	1	0	0	1	0	1	0	1	1	1	1	1	1	0	1	0	0	0	1	1	0	0	0	0	0	1
Wang et al., 2017[306]	1	0	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	n/a	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1
Lee et al., 2017[307]	1	0	1	1	1	1	1	1	1	1	1	0	0	1	0	1	1	1	0	1	1	1	1	1	1	1	n/a	1	1	1	1	0	0	1	1	1	1	1	1	0	0	0

APPENDIX – E: SUPPLEMENTARY MATERIAL FOR PERSONALISED TOTAL NEOADJUVANT THERAPY (PTNT) FOR ADVANCED RECTAL CANCER: A PROSPECTIVE COHORT STUDY WITH TAILORED TREATMENT SEQUENCING BASED ON CLINICAL STAGE AT PRESENTATION

Personalised Total Neoadjuvant Therapy (pTNT) for Rectal Cancer – Royal Adelaide Hospital Protocol

All patients who undergo TNT must be entered into a prospective database with local ethics approval to monitor compliance and measure patient outcomes.

Distant failure risk (need for systemic control)
Patients with liver / lung metastases, EMVI, abnormal mesorectal or lateral pelvic nodes on MRI.

- **Induction Chemotherapy** 16 weeks
    - 8 cycles mFOLFOX6, second weekly for 16 weeks (or 6 cycles CAPOX for 18 weeks).
    - Oxaliplatin, 85 mg/m^2 IV infusion, Calcium Folinate (Leucovorin) 50mg IV bolus, Fluorouracil 400 mg/m^2 IV and 2400 mg/m^2 CIV via pump over 46 hours.
    - CT chest/abdo/pelvis halfway (after 4 cycles): if poor local response or progression ➔ consider accelerating to CRT early (rediscuss at MDT).
- **Wait** 2 weeks after completion of all chemotherapy doses
- **Long course CRT** 6 weeks
    - 50.4 Gy external beam modulated radiation in 25 fractions over 5 weeks.
    - Consider dose escalation to 54 Gy in 27 fractions for those who wish to push for cCR (e.g. when functional outcomes unacceptable).
    - 5FU infusion via pump for the period, or capecitabine orally 5 days per week
- **Wait** 10 weeks
    - Liver resection in wait period if indicated
    - CT C/A/P near conclusion of wait (around 8 weeks) to assess distant disease
    - Flex sig near conclusion of wait (around 8 weeks) to assess clinical response.
        - If cCR suspected => repeat MRI to complete cCR assessment
        - If no cCR => proceed to surgery

Loco-regional failure risk (need for local control)
Patients with bulky local disease, T4 extension, low tumours.
(This may also include patients with earlier stage disease who decline upfront surgery).

- **Long course CRT** 6 weeks
    - 50.4 Gy external beam modulated radiation in 25 fractions over 5 weeks.
    - Consider dose escalation to 54 Gy in 27 fractions for those who wish to push for cCR (e.g. when functional outcomes unacceptable).
    - 5FU infusion via pump for the period, or capecitabine orally 5 days per week
- **Wait** 2 weeks after completion of radiotherapy
- **Consolidation Chemotherapy** 16 weeks
    - 8 cycles mFOLFOX6, second weekly for 16 weeks (or 6 cycles CAPOX for 18 weeks).

- Oxaliplatin, 85 mg/m^2 IV infusion, Calcium Folinate (Leucovorin) 50mg IV bolus, Fluorouracil 400 mg/m^2 IV and 2400 mg/m^2 CIV via pump over 46 hours
- CT chest/abdo/pelvis halfway (after 4 cycles): if poor local response or progression ➔ consider accelerating to surgical resection (rediscuss at MDT)

- **Wait** 4 weeks
  - Flex sig near conclusion of wait (around 2 weeks) to assess clinical response.
    - If cCR suspected => repeat MRI to complete cCR assessment
    - If no cCR => proceed to surgery

Distant and loco-regional failure risk

- Favour induction chemotherapy, but decision on a case-by-case basis.

Non-Operative Management (NOM) Protocol ("Watch and Wait")

This is offered to patients who achieve complete clinical response (cCR).

Diagnosis of cCR

- **Rectal exam:** No palpable tumour (when one was initially palpable)
- **Flexible sigmoidoscopy:**
  - No visible tumour AND White scar
  - (negative biopsies from scar not mandatory)
- **MRI pelvis:** TRG 1 or 2
  - Substantial downsizing with no residual tumour
  - OR residual fibrosis only
  - OR residual wall thickening due to oedema with fibrosis
  - AND No suspicious lymph nodes / EMVI

Active surveillance for 5 years (with patient consent)

- **Rectal exam, flexible sigmoidoscopy, and CEA** every 3 months for the first 2 years, then every 6 months for a total of 5 years (scar biopsy not required unless suspicion of regrowth).
- **MRI pelvis** every 3 months for 1 year, and then 6 monthly for 5 years.
- **CT chest/abdomen** every 12 months for 5 years
- **Colonoscopy** at 1 year (then 6 and 11 years as per usual colorectal cancer surveillance)

Appendix

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- Scott Carruthers (Radiation oncologist, RAH)

Aim

- Maximise chemotherapy compliance in patients with advanced rectal cancer.
- Improve disease free survival and potential for organ preservation.
- Bring practice in line with current evidence on rectal cancer treatment.

Rationale

- Biological plausibility that administering systemic treatment upfront may maximise DFS / OS in patients with high risk of distant failure.
- Biological plausibility that administering additional treatment in the neoadjuvant setting will increase the rates of complete clinical response of the primary rectal cancer, and potential for organ preservation.
- Recent level 1 (abstract) and level II evidence which supports the above (see references below).

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