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Leiden
The Netherlands

Towards implementation of the tumour-stroma ratio in colorectal cancer

Polack, M.

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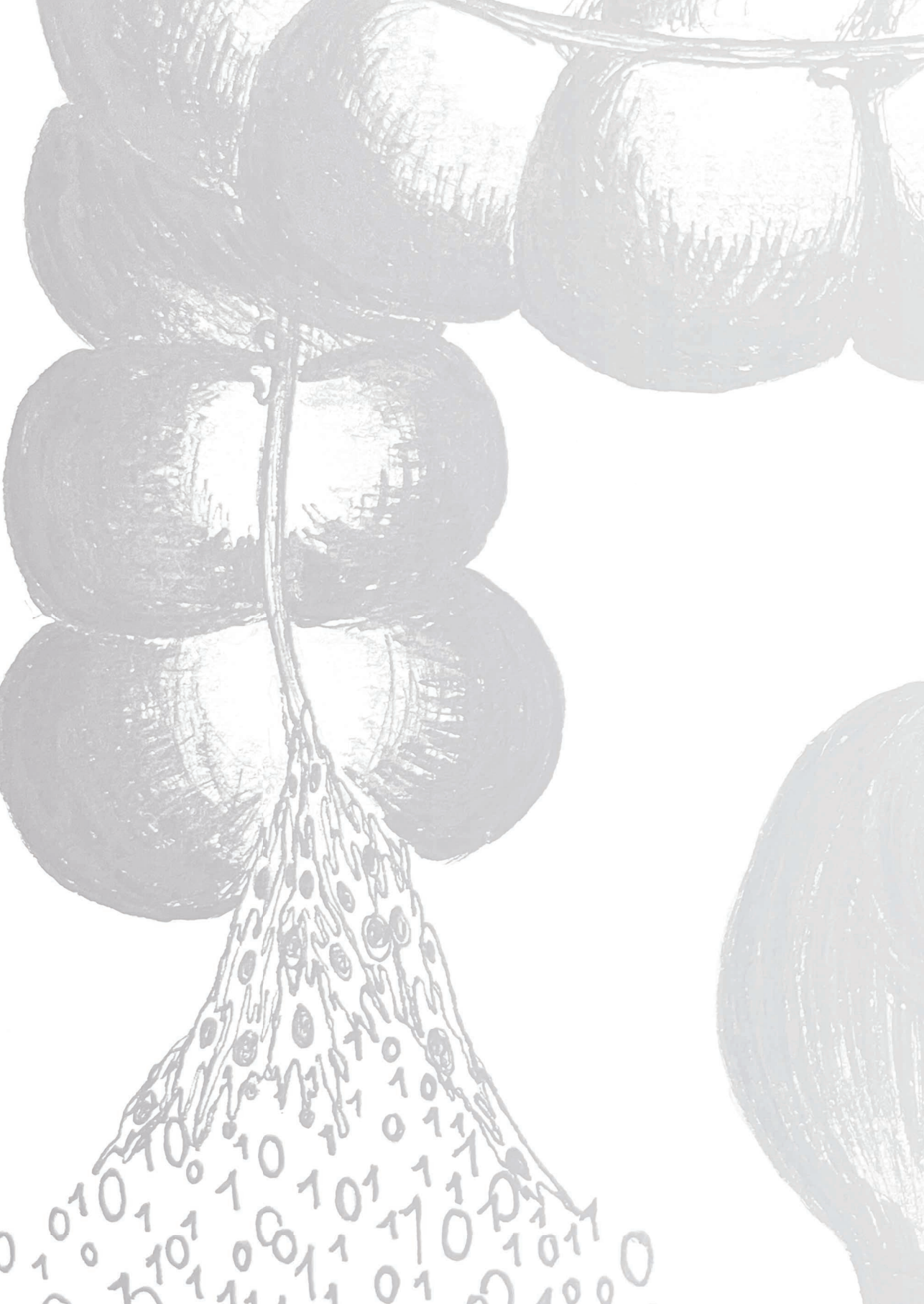

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Chapter 1

General introduction and thesis outline

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Colorectal cancer has remained the third highest cancer type in incidence and second cause of cancer-related deaths for years all over the world [1-3]. The cornerstone of international treatment guidelines encompasses disease extent, defined by the tumour-node-metastasis (TNM) classification [4, 5], and other assessments regarding expected patient-related outcomes, such as survival and treatment benefit [6-9]. However, recurrence rates as well as heterogeneity in survival outcomes of colorectal patients with similar TNM-stages are illustrative of a currently suboptimal therapy selection, leading to high occurrences of overtreatment and undertreatment. Moreover, even a survival paradox is observed, where patients with lower, less extensive disease and theoretically thus more favourable, TNM-stages, have a conversely worse survival outcome [6, 8, 10, 11]. Therefore, improving the prediction of patient-related outcomes and thus therapy selection is imperative.

In an attempt to attain this improvement, many histopathological parameters and biological markers (biomarkers) have been discovered and developed [12, 13]. Microsatellite instability (MSI) status, tumour deposits and tumour budding were for instance relatively recently implemented in routine pathology diagnostics [6, 14-16]. Whereas these mainly pertain to the tumour epithelial compartment, i.e. the neoplastic cells, this traditional tumour epithelium-centred approach remains therefore insufficient. It is pivotal to expand our current focus to include parameters that enable more accurate predictions and a personalized treatment strategy. Hence, the paradigm is shifting, with the surrounding tumour microenvironment increasingly emerging as an important modulator and no longer deemed an innocuous substance.

Tumour microenvironment

The past decades, the complex crosstalk between the tumour epithelial compartment and tumour microenvironment has piqued the interest of researchers worldwide [17-20]. Although the exact mechanism is yet to be elucidated, it has become apparent that this dynamic entity, predominantly comprising immune cells, extracellular matrix, vasculature and fibroblasts with various forms and functions, modulates tumour behaviour [21-23]. The tumour stroma therein, especially an abundance of stroma, has furthermore been observed to be of detrimental influence and enhances aggressive characteristics, such as tumour invasion and therapy resistance [22, 24-27]. The tumour-stroma ratio (TSR), i.e. the proportion of the tumour epithelial compartment compared to the tumour stromal compartment expressed in percentages and the main focus of this thesis, captures this effect specifically.

Tumour-stroma ratio

Since the first publication of this histological parameter in 2007 by our research group [28], the TSR has been protocolized [29, 30], promoted [31, 32] and proven [33-36], as well by other researchers [24, 37-39] and in multiple cancer types [40-42]. Iteratively, stroma-high (>50% intratumoural stoma percentages) tumours indeed lead to significantly worse patient-related outcomes than their stroma-low (≤50% intratumoural stroma) counterparts. A proposal to implement the TSR as additional biomarker in international guidelines and pathology diagnostics was thus presented to the TNM evaluation committee of the Union for International Cancer Control (UICC) and College of American Pathologists (CAP). While the advocated-to instances endorsed the potential of the TSR and despite this overwhelming evidence, however, a prospective study was still considered necessary. In a complying response, subsequent to an international consensus with support of the European Society of Pathology (ESP) and establishment of an official TSR-scoring E-learning [43], the multicentre UNITED study (Uniform Noting for International application of the Tumour-stroma ratio as Easy Diagnostic tool) was therefore initiated [44]. This thesis presents the results of the UNITED study in **Chapter 2**, validating the prognostic value of the TSR as biomarker on disease-free survival in colon cancer patients (DFS) [45].

Colon cancer vs. rectum cancer

Albeit often collectively termed, rectal cancer is a different entity than colon cancer [9, 46]. Treatment of rectal cancer varies thus from that of colon cancer, with a large focus on organ-sparing approaches [9, 47]. 'Neoadjuvant therapy' (Latin: *neo* = new, *adjuvare* = to help), first used to describe therapy intended for too extensive primary tumours for surgery [48], is a pillar in treatment in rectal cancer currently. Where it was initially implemented to enhance local control in addition to the total mesorectal excision (TME) [49, 50], research has shown that more intricate regimens can induce a complete response, potentially rendering surgery redundant [47, 51, 52]. However, this response is prone to variety and a large heterogeneity is seen between clinical and pathological responses (cCR and pCR, respectively) [53-56]. Upfront selection of patients standing to benefit from neoadjuvant therapy, and patients who should potentially not undergo a 'watch-and-wait' strategy [57], is thus essential.

The TSR has been shown previously to not only be a prognostic biomarker, but also to predict response to treatment [58-60]. Since neoadjuvant therapy alters the tumour microenvironment [61-63], resulting in e.g. fibrosis, this leads to inconclusive TSR scores after treatment. Scoring the TSR in the biopsies has previously proven to be representative for the TSR score of the primary tumour and, moreover, a predictive biomarker [64, 65], although large, multicentre studies evaluating the potential of the TSR in

predicting neoadjuvant response in rectal cancer are lacking [66-68]. In **Chapter 3** therefore, we integrate two large, clinical trials (RAPIDO [53] and PROCTOR-SCRIPT [69]) with our LUMC cohort and aimed to validate the predictive value of the TSR in rectal cancer.

Stromal fibroblasts and lymph node metastasis

Initial cancer diagnosis and staging, especially lymph nodes, continues to be challenging with the current CT and MRI scanning per protocol [6, 70]. PET scanning, a modality where anatomical and physiological functions are combined by using radioactive fluor-labelled fluordeoxyglucose ([18-F]-FDG), is not commonly used in routine work-up and has pitfalls as well [6, 71, 72]. Cancer-specific tracers are increasingly researched, for which, targets pertain to the tumour stroma as well. Despite the large heterogeneity tumours are prone to, the tumour stroma generally contains quiescent fibroblasts, which can be activated through many pathways, giving rise to cancer-associated fibroblasts (CAFs) [73, 74]. Due to their tumour promoting functions, these CAFs are considered intriguing targets, and as such, a universal and high potential CAF marker has been identified: fibroblast activation protein (FAP) [75-77]. Coupled with a radioactive label, the fibroblast activation protein-inhibitor (FAPI) is exponentially subject to research in radiological imaging as tracer with FAPI-PET/CT scans, aiming to ascertain improvement to current imaging protocols [78-81]. Ultimately, tumour-targeted tracers can even be applied in a theragnostic sense [82-85]. Much research is done currently on the FAPI-tracer, although correlation studies with the golden standard, i.e. pathology, are lacking [86, 87].

As the importance of the TSR in lymph nodes metastases has been proven previously [88, 89], first, a theoretical framework for lymph node metastasis, specifically the stromal assessment, was established (**Chapter 4**). Here, we describe the tumour stroma in lymph node metastases in detail and expand on our TSR measurements, to support future correlation research between FAPI uptake on PET/CT scanning with the pathological lymph node assessments [90]. Moreover, as the CAFs had been identified as crucial modulators in the tumour behaviour of CRC, in **Chapter 5** we performed a large histological comparison between the traditional haematoxylin and eosin (H&E-)stained slides and immunohistochemical staining for FAP in CRC, biopsies and resected material with primary tumour and lymph nodes. As FAP constitutes an attractive marker for improved diagnosis through FAPI imaging, and translational studies are scarce, we aimed to describe the patterns to form a biological background for future clinical studies and ascertain correlation to the TSR.

Digitalisation and artificial intelligence

Historically, as the breakthrough that shaped the modern pathology from the mid-nineteenth century onward, the microscope has been the golden standard modality and trusted technique for the specialty [91, 92]. Glass slides containing tissue are visualized and analysed through Bright-field light microscopy in routine diagnostics, however, digitalisation is gaining interest in pathology [93]. Slides are increasingly scanned, resulting in digital whole slide images (WSIs). Initially intended to decrease workload and enable remote working for pathologists, these WSIs can also be analysed by computers, for instance by using artificial intelligence algorithms [94-96]. Often criticized and characterised as a 'black box', **Chapter 6** attempts to elucidate this phenomenon, where, in contrast to training on time-consuming annotations like in supervised deep learning to automate e.g. TSR scoring [97-99], we trained a state-of-art self-supervised deep learning model on unannotated WSIs [100]. Small image patches (tiles) from these WSIs were grouped based on similar histological patterns by this model, forming histomorphological phenotype clusters (HPCs). We subsequently analysed the HPCs and correlated these to patient-related outcomes, providing novel insights in potential histological aspects with the emphasis on tumour stroma, and advocate their clinical relevance.

Summary and discussion

The presented research in this thesis is ultimately summarized and followed by a discussion where future perspectives of research and more specifically, concrete and necessary steps are described towards the imperative implementation of the TSR as additional biomarker in guidelines and pathology routine diagnostics (**Chapter 7**). This thesis is concluded by the summary and discussion translated in Dutch and other appendices.

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