New insights in pelvic anatomy and implications for radical nerve-sparing pelvic surgery. From microscopy to a virtual 3D anatomical atlas

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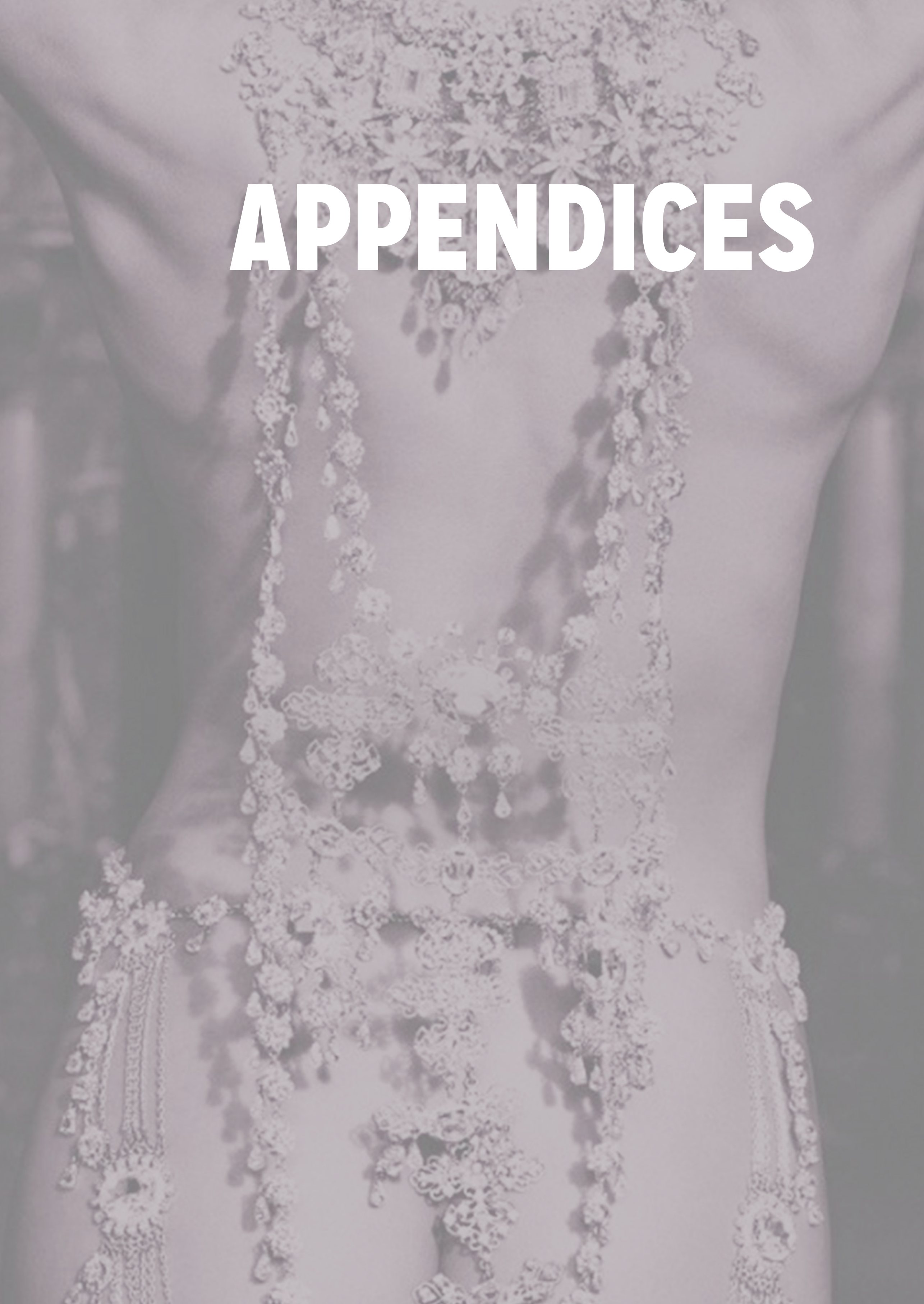
APPENDICES



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Discussion and future perspectives

Anne C. Kraima

Over last decades, the treatment and outcomes of rectal cancer have markedly improved. Total mesorectal excision (TME) has been globally adopted as the golden standard in the surgical treatment and involves radical *en-bloc* resection of the diseased rectum and surrounding mesorectum as a complete package with an intact mesorectal fascia, showing no perforations, disruptions or tears.[1-4] The strongest predictor for recurrent disease is tumour involvement of the circumferential resection margin (CRM), emphasizing the need to completely remove the rectum and mesorectum.[5]

Nowadays, rectal cancer management relies on adequate teamwork in which surgeons, radiologists and pathologists join forces. The role of the radiologist is important as preoperative imaging assesses the tumour's distance to the mesorectal fascia and selects patients in whom the CRM is potentially involved and conventional TME surgery is unlikely to offer curation.[6, 7] These tumours are usually locally-advanced and extend far into the mesorectal fat or penetrate the mesorectal fascia. Recently, the MERCURY (Magnetic Resonance Imaging and Rectal Cancer European Equivalence) study group has showed that high-resolution magnetic resonance imaging (MRI) preoperative assessment of the CRM status (cut-off ≤ 1 mm) is superior to the classical American Joint Committee on Cancer TNM-based criteria[8] for assessing the risk of local recurrences and subsequent survival.[9] Neo-adjuvant therapy might downsize and –stage these tumours after which curative surgery is feasible.[10] The principle aim of TME surgery is complete resection. Local recurrence is considered as a failure of complete surgical removal of the tumour. Thus, the quality of the operative procedure performed by the individual surgeon represents one of the most important prognostic factors.[11, 12]

The quality of TME surgery can be controlled by pathological evaluation of the resection specimen.[13] To date, pathology has been integrated as a part of rectal cancer treatment in clinical trials, but it has not been routinely introduced in daily clinical practice. Quirke et al.[14] evaluated the effect of the achieved surgical plane on the oncological outcomes by using a three-point grading system. Specimens having a smooth mesorectal surface with only minor irregularities (tears in the mesorectal fat of less than 5 mm) and no distal conisation were graded as being surgically dissected in the 'mesorectal plane'. If the specimen had a moderate bulky mesorectum, revealing an irregularity of the mesorectal fat with moderate distal coning, the surgical plane was classified as the 'intramesorectal plane'. In case of a little bulky mesorectum and defects down to the muscularis propria, the achieved surgical plane was graded as the 'muscularis propria plane'. These planes reflected good, moderate and poor quality TME surgery, respectively. It was shown that the plane of surgery did not deteriorate with advancing of the TNM-stage, suggesting that the plane of dissection is determined by the ability of the individual surgeon to actually find the proper plane.[14] Hence, surgery remains the cornerstone in the multidisciplinary treatment of rectal cancer.

Good-quality TME surgery comprises correct mobilisation of the posterior, lateral and anterior mesorectum by dissection in the 'holy plane'. According to Heald et al.,[1-3] radical *en-bloc* removal of the complete rectum and mesorectum, which are one distinct lymphovascular entity, can be achieved by dissection along the pelvic fascia surrounding the embryological hindgut. In contrast to Pannett,[15] Heald et al.[1-3] did not believe that the pelvic fascia was an impenetrable barrier for the spread of rectal cancer, but that it rather formed an avascular interface between the viscus and soma. Shortly later, it was reported[1] that dissection in the 'holy plane' simultaneously enables preservation of the pelvic autonomic nerves. The introduction of the 'holy plane' of TME has evoked a re-evaluation of the surgical anatomy and embryology of the rectum as it was internationally agreed on that excellent anatomical understanding was fundamental to successfully perform TME surgery. Many researchers have focussed on defining the anatomical basis of TME surgery, leading to more awareness of the difficult anatomy of the rectum. Together with surgical training this has reduced local recurrence rates and improved survival, pointing out the fundamental role of surgical anatomical education.[16-18] Despite these improved surgical outcomes, the numerous anatomical descriptions concerning the arrangement of the pelvic fascia and the pelvic autonomic nerves were conflicting.[19-31] In the literature, the surgically famous 'holy plane' has been frequently contradicted of which some researchers have claimed that an additional layer of fascia runs between the visceral and parietal fasciae.[23, 27] The ongoing discussion on the intricate arrangement of the perirectal fascia (the part of the pelvic fascia surrounding the rectum) and autonomic nerves has hampered defining uniform anterior, lateral and posterior dissection planes. Many researchers tried to reveal delicate anatomy by cadaveric dissections or in vivo surgical observations.[20, 21, 24, 26, 27] The main drawback to investigating the macroscopic anatomy of the perirectal fascia in this way is that cadaveric dissection of an area rich in dense connective tissue leads to the creation of artefacts. Indeed, the numerous anatomical descriptions of the perirectal fascia,[20, 23, 27, 31, 32] Denonvilliers' fascia (DVF),[24, 28, 30, 33-35] and the lateral ligaments[32, 36-38] are contradicting. This delicate anatomy must be microscopically studied, preferably in whole mount microscopic sections so to investigate topological relationships as well.

In this thesis, the intricate arrangement of the perirectal fascia and the pelvic autonomic nerves along the rectum is elucidated by microscopic analysis of four cadaveric *en-bloc* pelvic specimens. The fasciae posterolateral to the rectum appeared as a multi-layered envelope in which several laminae merged with the mesorectal and parietal fasciae. This means that radical removal of the rectum is merely feasible by dissection on the mesorectal fascia, which is in full agreement with Heald et al.[1, 2] It must be questioned whether the contradicting results of the few studies who actually did investigate the arrangement of the perirectal fascia and autonomic nerves microscopically,[23, 25, 31] are misinterpretations caused by analysing only small microscopic sections without including topographical relations or are representations of anatomical variations. The time-consuming process of producing whole mount microscopic sections along the complete length of the rectum restricted us to investigate only four cadaveric specimens. However, the constant location of the autonomic nerves directly lateral to the mesorectal fascia indicates that radical TME surgery together with autonomic nerve preservation is only feasible by dissection on the mesorectal fascia. The individual surgeon might wish to dissect sharply as electrosurgical dissection could damage the nerves either way. Mobilisation of the anterior rectum in TME involves dissection along DVF. Due to its central position between the seminal vesicles and prostate (or vagina) and anorectum, it also has an important functional role in benign urologic, gynaecologic and anorectal pathology. DVF is one of the most frequently studied structures in the pelvis. This thesis outlines the historical, anatomical and surgical context of the debate on DVF so to provide insight why DVF has become a puzzling structure to most urologists, gynaecologists and rectal surgeons. Many researchers interpreted first hypotheses on DVF, based on poor histological evidence, as proven facts and failed to accurately examine the microscopic anatomy themselves. In whole mount microscopic sections, this thesis has proven that DVF forms a macroscopic entity of compressed collagenous layers adjacent to the anteriorly located prostatic fascia (or posterior vaginal wall) and the posteriorly located mesorectal fascia. To put it simply, there are no layers distinguishable on a macroscopic level and surgeons aiming to 'split the layers' of DVF might end up in resecting too much anterior or posterior tissues or damaging urogenital and anorectal organs. Given the small number of histologically analysed English cadaveric specimens, one might argue that these results should be interpreted with caution as, for example, ethnical differences or effects of the amount visceral fatty tissue cannot be ruled out. Nevertheless, the descriptions are in line with those provided by Villers et al.,[39] who histologically investigated 243 radical prostatectomy specimens and noted that DVF formed a continuum with the prostatic fascia. It was concluded that in case of larger tumours DVF should also be removed to not comprise radical surgery, which is equivalent to the principles in TME surgery.

Furthermore, this thesis has shown that the mesorectal fascia, at least in the four cadaveric English specimens, has a variable appearance with regard to its thickness and completeness, most prominently at the anterolateral mesorectum. Solely by investigating its microscopic anatomy, the unpredictability of the mesorectal fascia and consequent mesorectal plane was revealed. Surgeons often mention that finding the correct dissection plane is quite straightforward at the upper- and mid-rectum, but the plane gets easily lost while dissection proceeds caudally at the anterolateral low rectum. To fully reveal the surgical caveats, the anatomy has to be effectively studied on a microscopic level.

The aforementioned anatomical insights raise further questions. Quirke et al. showed 3-years local recurrence rates of 4% (mesorectal plane), 7% (moderate plane) and 12% (muscularis propria plane) in patients with a tumour-free CRM.[14] These numbers are satisfying and clearly underline the importance of good-quality TME surgery together with pathological evaluation. It would be interesting to concentrate on the small group of patients in whom surgery was optimal, i.e. achievement of a superior surgical plane and negative CRM, but who still developed a local recurrence. Interestingly, local recurrences were associated with tumours in the anterior quadrant.[14] Could the unpredictable appearance of the mesorectal fascia, being most prominent at the anterolateral mesorectum, have played a role in facilitating microscopic tumour spread beyond the borders of the mesorectum? The additive benefit of short-course preoperative radiotherapy in these patients, leading to a 3-years recurrence rate of 1%, shows that there might be an additional anatomical factor potentially affecting the outcomes. This thesis illustrates the fundamental importance of investigating and understanding the microscopic anatomy of the perirectal fascia. To get a comprehensive view on the anatomical variation across a population, more cadaveric *en-bloc* specimens need to be studied in the future. The hypothesis that the perirectal fascia originates from loose mesenchyme undergoing morphological changes during growth and distension of the rectum,[40, 41] is also supported in this thesis. As early as 1950, Hayes already stressed that sharp lines of demarcations of the perirectal fascia cannot be demonstrated.[41] Remarkably, studies re-evaluating either microscopic or macroscopic anatomy of the rectum have merely focussed on defining anatomical planes and spaces without bearing in mind that this delicate anatomy might not be delineable. Moreover, additional effects of age, gender, body mass index, ethnicity and preoperative radiotherapy on the perirectal fascia are yet to be discovered. All these factors could potentially affect the loose mesenchyme, making up the perirectal fascia, and should be microscopically studied to advance the understanding of how (pathological) anatomy influences the treatment of rectal cancer. In daily clinical practice, surgeons need point to point descriptions that help them to find the correct planes, taking into account the technical difficulties of operating in the narrow and deep pelvic cavity together with the often bloody surgical field. However, such practical descriptions can only guide surgeons safely if the detailed anatomy of the perirectal fascia is fully understood.

Low rectal cancer is world-wide a challenging disease. Multiple studies have shown that adominoperineal excision (APE) is associated with higher rates of tumour involvement of the CRM, tumour perforation and incomplete surgical removal when compared with anterior resection for more superior tumours.[42-45] The need to improve the surgical techniques of APE has been acknowledged to ameliorate the outcomes. Tumours located near the puborectalis muscle, where the mesorectal fascia blends with the parietal fascia, are at highest risk for an incomplete resection. The conventional APE specimen is classically waisted at the level of the puborectalis muscle.[46] As a consequence, the anatomical and surgical planes surrounding the low rectum and anal sphincter complex have been re-examined and defined to indicate the quality of the surgery.[47, 48] Good surgery is carried out by dissection in the extralevator plane, producing a cylindrical specimen in which the levator ani muscle is removed *en*-bloc with the rectum and mesorectum and no defects deeper than 5 mm are encountered. The surgery is qualified as being moderate when dissection has taken place in the intersphincteric plane, creating a CRM on the surface of the sphincter muscles. Such a specimen typically shows waist formation but the anal sphincter muscles are intact. Poor surgery is characterized by severe irregularities on the surface of the specimen, exposing the muscularis propria or internal anal sphincter or even showing perforations to the lumen.[47] The extralevator APE is preferred over the conventional APE in distal tumours located near the puborectalis muscle as it leads to a reduction of the involved CRM rates, tumour perforation rates and local recurrence rates.[49-51] Recently, a systematic review and meta-analysis have confirmed these outcomes and have also showed that the quality of life after extralevator APE is not inferior to the conventional APE.[52] From an anatomical point of view, APE is more difficult than anterior resection because the anorectum needs to be detached from the perineal body. The perineal phase of an APE is most challenging as there is no natural dissection plane through or around the perineal body.[53] Any deviation might end up in moderate or poor quality surgery or damaging the urogenital organs. In case of an intersphincteric resection, dissection is deliberately carried out in between the internal and external anal sphincter. By generating the intersphincteric plane, surgeons aim to preserve the external anal sphincter and subsequent fecal continence. Remarkably, not a single study reporting on the technique of intersphincteric resection has felt the urge to study the microscopic anatomy of the anal sphincter complex. It is very important to understand the potential pitfalls when the intersphincteric plane is being generated.[54-58] In short, the trend of re-evaluating the rectal anatomy after the introduction of TME has not automatically led to a re-evaluation of the anal sphincter complex and perineal body. These structures have not been effectively described from the perspective of an oncological approach. To optimise the surgical technique and subsequent outcomes of low rectal cancer, this thesis fills this gap in the surgeon's knowledge by providing microscopic anatomical insight in the anal sphincter complex and perineal body. The previously underappreciated role of the longitudinal muscle in integrating the external and internal anal sphincters and anchoring the anorectum into the perineal body and levator ani muscle, has been unravelled. In addition to providing insight in the difficulties of surgical dissection of an area so highly integrated by penetrating smooth and striated muscle fibres, the results of this thesis reveal also important individual differences. By analysing solely six specimens, differences in the morphology of the longitudinal muscle and the presence of striated muscle fibres in the anal submucosa were brought into light. This is not only important to surgeons, as they should realise that the intersphincteric plane might be unpredictable, but this might have important consequences for the pathological staging of low rectal cancer and administration of adjuvant therapies. The penetrating muscle fibres in the anal sphincter complex form routes for infectious spread and fistulae extension in benign anal pathology,[59] raising the question if tumours could also spread in this way. If this is the case, pT1 low rectal tumours growing into the anal submucosa but not into the internal anal sphincters could be more invading than previously thought. Is it actually justified to stage anal cancer and low rectal cancer invading the anal sphincters in two different ways? To answer this question, the precise lymphatic drainage pathways of the anal sphincter complex must be studied. There is a need to investigate if lymphatics cross the different layers regardless of the embryologically defined mid- and hindgut. Forthcoming results will help to determine the evolution of a potential new staging system for low rectal cancer. Furthermore, future studies must address the presence of inter-individual differences in the anatomy of the anal sphincter complex across populations. The time-consuming process of histologically analysis whole mount microscopic sections of cadaveric specimens is limiting.

The introduction of TME surgery has made the individual surgeon realise that it is important to obtain both optimal oncological and functional outcomes while operating in the pelvis. If oncologically safe, surgical preservation of the pelvic autonomic nerves maintains postoperative anorectal and urogenital function.[60-62] Adequate functioning of pelvic organs requires combined action of the sympathetic and parasympathetic nervous systems with input from the somato and viscerosensory nervous system.[63] The pelvic floor is dually innervated by the pudendal and levator ani nerves.[64-66] The anal sphincter complex, urethral sphincter complex and external genital organs demand co-ordinated activity of both somatic and autonomic nerves to function sufficiently.[67-69] Thus, the neural innervation of the pelvis is complex. It is important to be aware of the neuroanatomical composition of the pelvic autonomic network, not only to understand the reasoning for surgical preservation but also to precisely inform patients about potential post-operative complications. This thesis has unexpectedly provided neuroanatomical evidence that damage of the superior hypogastric plexus and/ or hypogastric nerves might result in erectile dysfunction due to parasympathetic denervation. The neurochemical characterisation of the autonomic nervous system is not straightforward, because many neurotransmitters and – peptides are released or expressed in both sympathetic and parasympathetic nervous systems. To date, there is no antibody that exclusively marks post-ganglionic parasympathetic nerve fibres.[63] The antibody neuronal nitric oxide synthase, which is released from the terminals of parasympathetic nerve fibres to mediate erectile function,[63, 70] did not function in our post mortem tissues. Using triple-stains and human positive and negative controls, it was highly likely that parasympathetic nerve fibres do run in the superior hypogastric plexus and hypogastric nerves. The origin of these parasympathetic nerve fibres should be revealed by neuronal tracing studies. The concept of nerve-sparing surgery, as is being established in pelvic surgery, is also relevant for other surgical disciplines. Some studies have reported on the manifestation of erectile dysfunction after vascular surgery.[71, 72] Nerve-sparing surgical techniques for open abdominal aneurysm repair seem to be feasible,[73] but further research is needed to take this to the next level. Vascular surgeons must become aware of the functional impairments that may arise after nerve disruption in the peri-aortic compartment. A prospective study reporting on the occurrence of parasympathetic pelvic dysfunction in patients subjected to open abdominal aneurysm repair would be the first step.

Although the pelvic autonomic network has been studied extensively,[25, 74-77] the nerve branches from the inferior hypogastric plexus innervating essentially the pelvic organs have gained far less attention. The course of the neurovascular bundles in males is well-described, passing closely the seminal vesicles and prostate to innervate the bladder and penis, [78] but in females this is less known.[78] This thesis has revealed the presence of post-ganglionic sympathetic and parasympathetic nerve fibres surrounding the distal ureter. The risk of disrupting these nerve fibres is most significant to gynaecologists. Four types of radical hysterectomy techniques have been described by Querleu and Morrow.[79] In two types the ureter is completely mobilised, and in one type the ureter is unroofed and rolled laterally.[80] The presence of fine nerve branches in the deep layers of the vesico-uterine ligament, laterally and caudally to the ureter, has been previously acknowledged.[80-84] However, three-dimensional (3D) reconstruction of the fetal pelvic autonomic network as presented in this thesis clearly shows that these fine branches actually encircle the distal ureter and are situated in both superficial and deep layers of the vesico-uterine ligament. Preservation of this so-called vesical plexus is only achievable in one of the four types of radical hysterectomy according to Querleu and Morrow's classification.[79] Indeed, bladder dysfunction (urge incontinence, stress incontinence, difficulties in emptying the bladder and dysuria) is often reported following a Wertheim-Okabayashi radical hysterectomy, in which the ureter is completely mobilised.[85] Due to the restrictive use of immunohistochemistry in post mortem fetal material, we could not study sensory nerve fibres in the vesical plexus. Although the nature of the aforementioned postoperative bladder impairments presumes the presence of sensory nerve fibres in the vesical plexus, this is yet to be revealed.

Modern treatment of both rectal cancer and cervical cancer can be tailored to the individual patient's tumour characteristics. The principles of radical surgery are similar for both cancers. In radical hysterectomy, this entails *en-bloc* excision of the uterus and/or upper vagina together with surrounding parametrium and a pelvic lymphadenectomy. Several radical hysterectomy techniques have been reported,[80] differing mainly in the extent of parametrectomy. The extent to which the parametrium should be resected is still a matter of debate. This thesis has discovered that the lymphatic drainage pathways of the cervix uteri run via the cardinal ligaments (superiorly to the ureter) and the sacro-uterine ligaments. As cervical cancer can spread via lymphatics, these parts of the parametrium should be removed. In early stage cervical cancer, there might be no need to remove the vesico-uterine ligaments. Consequently, mobilisation of the distal ureter (disrupting the vesical plexus) might be avoidable. Although the exact lympathic drainage pathways of the cervix uteri must be confirmed in human adult tissue, this thesis has shown that the functional outcomes of early-stage cervical cancer could be further optimised.

Anatomically, the term *parametrium* is actually incorrect as it belongs to the endopelvic fascia that surrounds the uterus and upper vagina. This part of the endopelvic fascia has a more fibrous consistency and includes the broad ligaments, the cardinal ligaments, the sacro-uterine ligaments, the vesico-uterine ligaments and the paracolpal and paravaginal parametrium. The usage of this term could mistakenly lead one to believe that the parametrium forms a separate entity. Over the last years, Höckel and colleagues have advocated that locoregional cancer spread takes place in morphogenetic fields of embryonic development.[86, 87] A morphogenetic field represents a topologically defined tissue domain where malignant cells can survive, migrate and proliferate. In this perspective, it is believed that cervical cancer spreads in the Müllerian morphogenetic unit entailing the fallopian tubes (except fimbriae), uterus, vagina (except the distal part), mesosalpinges, mesometria and mesocolpia. The mesometria and mesocolpia in the Müllerian unit correspond to the broad ligaments, proximal parts of the sacro-uterine ligaments, rectovaginal ligaments, rectovaginal septum (Denonvilliers' fascia) and proximal uterine, vaginal arteries and veins.[88] Höckel projected the principles of TME surgery to the surgical treatment of cervical cancer and developed the total mesometrial excision (TMME).[89] In a group of 367 patients, who suffered from all stages of cervical cancer and underwent resection of the embryologically defined Müllerian unit and their associated lymphoid tissues, a locoregional tumour control at 5 years of 94% was achieved.[90] Although these numbers might support the ontogenetic theory of cancer spread in cervical cancer, there are some fundamental remarks to make that disfavour the concept of ontogenetic anatomy. Firstly, this thesis has shown that the lymphatic drainage pathways of the cervix uteri are not solely confined to the Müllerian morphogenetic unit. Lymph vessels draining the cervix uteri are connected with lymph vessels that drain the ureter, ovaries and fimbriae, revealing the course of lymphatics beyond the borders of one single morphogenetic unit. One could argue that the lymphatic flow might be restrained to one morphogenetic unit as this cannot be elucidated by immunohistochemistry. However, one lymphatic drainage pathway of the ovaries runs via the round ligament of the uterus to the inguinal lymph nodes. Clinical cases of inguinal metastases have been described in patients with ovarian cancer, suggesting that lymphatic flow might cross morphogenetic units as well.[91, 92] Secondly, normal developmental processes leading to growth of tissues and organs are controlled by embryological morphogenesis, which in ontogenetic anatomy are confined to a specific morphogenetic field. However, the ontogenetic anatomy does not focus on the development of the pelvic fascia or describes to which unit(s) the complete pelvic fascia would be confined to.[87, 89] For example, the Müllerian unit comprises only the broad and sacro-uterine ligaments. This make one to believe that the embryological morphogenesis in these parts would be different than in the cardinal and vesico-uterine ligaments. On contrary, it is most likely that the perirectal fascia develops by local mesenchymal condensation, resulting in at least some anatomical variation to a yet unknown extent. How could the development of the perirectal fascia, creating surgical spaces and planes, be translated to the development of morphogenetic units in ontogenetic anatomy? Most confusingly, there seem to be two different developmental theories that form the embryological basis for surgical concepts of treating malignant diseases in the pelvis. Future studies should further investigate the development of fasciae in the pelvis and examine how they contribute to the formation of compartments, which are used by surgeons. This thesis demonstrates the fundamental importance of investigating the microscopic anatomy of the pelvis. Only in this way essential anatomical details are revealed that have major implications for rectal and cervical cancer surgery.

Future perspectives

In daily clinical practice, surgeons must link general textbook anatomy and preoperative radiologic images to in vivo surgical anatomy. An experienced consultant surgeon might find this common practice and automatically translates two-dimensional (2D) anatomy to a 3D operative surgical field. A surgical resident, on the other hand, might struggle much more with interpreting the in vivo surgical anatomy correctly, specifically when it concerns the detailed anatomy of the pelvis, i.e. the intricate arrangement of the perirectal fascia and the autonomic nerves. Identification of the autonomic nerves is difficult and might be thwarted by patient characteristics such as gender and body mass index. Walsh et al.[78] has put it well by stating that *“we only see what we look for, but we only look for what we know.”* An excellent understanding of the aforementioned detailed pelvic anatomy must be part of every surgeon’s compendium in order to safely operate in the pelvis.

Over the last decades, laparoscopy has been progressively used in rectal cancer surgery. The MRC CLASSIC (Conventional versus Laparoscopic-assisted Surgery for Colorectal Cancer) trial was the first randomised controlled trial addressing the issue of laparoscopic rectal cancer surgery.[93] The 5-year analyses have demonstrated the oncological safety of laparoscopic surgery for rectal cancer as there were no differences between laparoscopic-assisted and open surgery in terms of overall and disease-free survival, and local and distant recurrences.[94] Bladder function was similar after laparoscopic and open TME surgery, but a trend towards impaired erectile function was reported.[95] This can probably be attributed to the proximity of the cavernous nerves to the lateral edges of DVF, which are prone to damage during anterior dissection. In the COREAN (Comparison of Open versus Laparoscopic Surgery for Mid or Low Rectal Cancer after Neoadjuvant Chemoradiotherapy) trial laparoscopic TME surgery provided similar disease-free survival rates in patients with locally advanced rectal cancer when compared to open TME surgery.[96] Recently, the COLOR II trial (Laparoscopic versus Open Rectal Cancer Removal) confirmed the oncological safety of laparoscopic TME surgery.[97, 98] The 3-years local recurrence rate was 5% for both laparoscopic and open TME surgery. In patients suffering from low rectal cancer, laparoscopic surgery was associated with a lower rate of tumour involvement of the CRM when compared to open TME surgery.[97] Although bladder and sexual impairments were reported after TME surgery, there was no difference between the laparoscopic and open approach.[99] Taking this all together, the progressive usage of a laparoscopic approach in TME surgery seems to be validated. However, laparoscopic TME surgery presents some surgical and technical challenges, which demand excellent anatomical knowledge.

The most important limitation in a laparoscopic approach is that surgeons are forced to rely on visual feedback rather than tactile feedback. The inability to palpate structures and the usage of instrumentarium via two or three ports are other limiting factors. The operative field is projected as a magnified and well-illuminated field on monitors, but these 2D projections may hamper the identification of specific detailed anatomy. Robotic-assisted surgery has been developed to overcome at least some of the limitations of laparoscopic surgery. Using robotics, more meticulous dissection might be possible resulting in less functional impairments. Currently, the da Vinci® surgical system is the only commercially available robotic system that is used in rectal, cervical and prostatic cancer surgery. Although robotic surgery is associated with increased costs and increased operating-time,[100] the oncological results seem satisfactory. A recent systematic review including 1229 patients of eight studies showed that robotic TME surgery results in lower conversion rates, lower CRM involvement rates and a lesser incidence of erectile dysfunction, when compared to laparoscopic TME surgery.[101] This systematic review concerned seven prospective or retrospective non-randomized controlled trials and only one randomized controlled trial including 66 patients. At the moment, the multi-centre randomized controlled ROLARR (Robotic versus Laparoscopic Resection for Rectal Cancer) trial is enrolling a target of 400 patients to perform a rigorous evaluation of the usage of robotic TME surgery in terms of technical feasibility and long-term oncological outcomes.[102] In early stage cervical cancer, the usage of robotic surgery seem to be safe and feasible as well.[103] The usage of robotics must be proven to be oncologically safe prior to implementing this technique in rectal and cervical cancer surgery. However, it will be inevitable that new technologies and techniques such as laparoscopic and robotic surgery will continue to be incorporated into surgical practice of rectal and cervical cancer. The individual surgeon is challenged to have optimal technical skills together with the capability to identify detailed pelvic anatomy on 2D projection monitors. Regarding the technical skills, there is a learning curve in laparoscopic and robotic rectal cancer surgery, which is often ill-defined with poor descriptions of mentorship and supervision.[104]

Accurate education is the key to enhance anatomical knowledge of the detailed pelvic anatomy among surgeons. There is a progressive need to have an excellent understanding of the anatomy given the current technological advancements that replace tactile feedback for visual feedback. In several Dutch hospitals, the majority of the colorectal cancer patients is primarily treated by laparoscopic surgery. As a consequence, the individual surgeon is challenged to find the correct anatomical planes by looking at a 2D projection monitor. The goal of accurate education must be to help surgeons to link 2D anatomy to 3D anatomy, making them safely rely on visual feedback. The first and second part of this thesis show that specific parts of the pelvic anatomy must be studied microscopically in order to understand the surgical pitfalls when operating in the pelvis. Part three of the thesis discusses how essential macroscopic and microscopic anatomy can be educated to surgeons.

Virtual reality training is a popular method to teach surgical trainees in laparoscopic surgery. It has proven to be beneficial in terms of reduced operating time and improvement of the operative performance of surgical trainees with limited experience in laparoscopy.[105] Up to now, surgical training curricula have focused mainly on the acquisition of technical skills rather than creating awareness of specific surgical situations. The latter is very important as surgical errors are more likely to result from perceptual or decision-making errors than from technical errors.[106] In this thesis, a virtual 3D anatomical atlas of a female pelvis was developed showing the essential detailed pelvic anatomy. By using a newly developed software program, which was capable of integrating heterogeneous anatomical data, one single anatomical atlas was created of the female pelvis: "the Virtual Surgical Pelvis" (VSP). The VSP has a great educational potential as it can be interactively explored online, making it easy accessible world-wide. The essential anatomical relationships between fasciae, autonomic nerves and blood vessels can be visualised in synchronously linked 2D and 3D views. This might be helpful for surgical trainees to see how the 2D anatomy relates to the 3D anatomy. Where previous 3D pelvic models show generic anatomy, the VSP can be registered onto patient-specific MRI scans, creating a patient-specific 3D model. The autonomic nerves are not visible on the current high resolution MRI. As a proof of concept, risk zones in which autonomic nerves are prone to surgical damage, were mapped onto a patient-specific MRI scan. Subsequently, the patient's MRI scan can be enriched with the registered risk zones or a 3D patient-specific model can be generated. Either way, specific situational awareness can be established if this is used in a preoperative setting as a surgical planning tool. Patient-specific 3D tumour reconstruction could improve the preoperative patient informing as to what postoperative complications might be expected. For example, the closer a tumour is located to the anal verge, the more likely the patient develops sexual dysfunction.[107] 3D visualisation of the tumour's distance to the anal verge and surgical dissection planes can give both patients and surgeons better anatomical insight. In laparoscopic and robotic surgery, a 3D anatomical atlas has great potential to provide the anatomical context and guide surgeons through the operative procedure. Besides, it can be used in virtual reality surgical simulation applications.

Additionally, a 3D virtual anatomical atlas can be of major value in other preoperative and operative settings. In radiotherapy planning, the tumour is delineated based on the anatomical information obtained from MRI. The patient's MRI scan could be enriched with anatomical data captured in the VSP, facilitating the delineation of the radiation field. In image-guided surgery, an anatomical atlas would be of potential value to provide a comprehensive anatomical context when imaging vital structures or tumour.[108]

As discussed in this thesis, there are still important steps to make prior to integrating a 3D anatomical atlas in clinical surgical practice. Most importantly, an automatic segmentation tool must be developed to allow quick segmentation of patient-specific MRI scans and registration onto the anatomical atlas. Also, the essential male pelvic anatomy must be segmented and reconstructed to incorporate a male pelvis in the VSP. However, a novel and solid method to develop a 3D virtual anatomical atlas has been established. Future studies should primarily focus on further enriching the atlas with anatomical data, integrating it in medical curricula, offering it as an educational tool to surgical trainees, and validating its usage in clinical practice.

Nowadays, radical nerve-sparing pelvic surgery increasingly takes place in a technologically driven field. Advancements in either open, laparoscopic or robotic surgery are inextricably linked to the individual surgeon's knowledge of the complex pelvic anatomy. To be fully aware of the caveats during surgery, an excellent understanding of the microscopic anatomy is necessitated. Surgical anatomical education is essential to optimise treatment and improve the patient's outcomes. A 3D virtual anatomical atlas has great potential in educating surgical trainees by creating the bridge between 2D and 3D anatomy. In addition, it can provide the anatomical guidance in current and future technologically driven surgical fields.

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