Ⅴ．研究成果の刊行物・別刷

呼吸器外科 Knack & Pitfalls

専門医のための呼吸器外科の要点と盲点【I】

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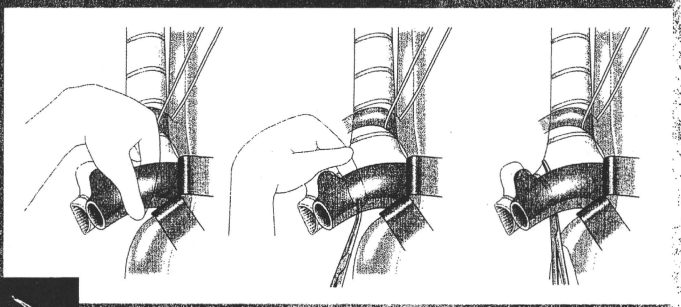

5．胸腔ドレナージ

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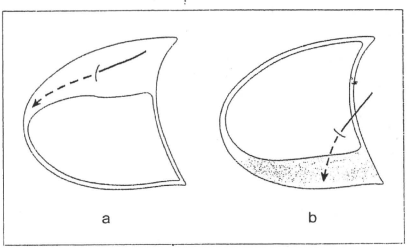
1. 胸腔ドレナージ

胸腔ドレナージは一見簡単なようでむずかしい手技である．なぜなら胸腔ドレーンは目的とする位置に正確に先端を留置しないと十分な目的を果たせないにもかかわらず，開胸時は別として通常は胸腔内の状況を頭の中で想像しながらドレーンを適正な位置に誘導する必要があるためである．胸腔ドレナージの手技は air をドレナージする場合と胸水をドレナージする場合では手技や留意点が異なるため，別々に解説する．



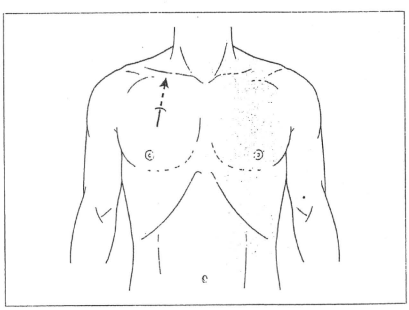
［図 1］有効なドレーンの留置法
air のドレナージは胸腔の前方を通って肺尖部にチューブを留置する（a）．胸水のドレナージは横隔膜より少し上のレベルの傍椎体部にチューブを留置する（b）．

2. 気胸のドレナージ法

1 考え方

air を有効にドレナージするためには，ドレーン先端はできるだけ胸腔の前方を通って肺尖部に留置する必要がある（図 1a）．肺尖部に最短距離で到達できるのは鎖骨中線上第 1 ～ 2 肋間あたりからドレーンを挿入する方法であるが（図 2），大胸筋を貫いてドレーンを挿入する必要があることと，創が前胸部の目立つ位置にできるため美容的にもよくないことから，筆者は腋窩部前方からドレーンを前胸壁に沿うようにして挿入し，先端を肺尖に留置するようにしている．もちろん気胸のドレナージキットのように前胸壁から挿入するように作成されたものは別である．

仰臥位にて患側上肢を挙上した体勢で，腋窩部の大胸筋外側縁後方で，前腋窩線上第 3 ～ 4 肋間あたりに相当する位置からトロッカードレーンを挿入する（図 3）．下部肋間からの挿入は肺尖からの距離が遠くなり不利であるし，ドレーンが葉間に入ってしまい利かなくなることもしばしばあり，気胸のドレナージとしては適切でない．



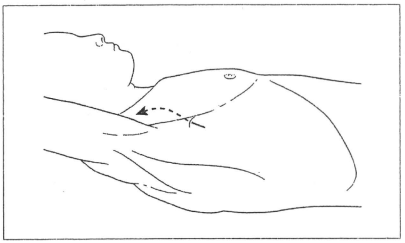
［図 2］前胸壁から肺尖部へのドレーン挿入法
肺尖部に最短距離で到達できるのは鎖骨中線上第 1 ～ 2 肋間あたりから大胸筋を貫いてドレーンを挿入する方法である．

ドレナージチューブの太さは，脱気が目的の場合，16Fr程度の細いものでも十分であるが，特発性血気胸のように血性胸水も多く貯留している場合には，ドレーンが凝血で閉塞する可能性を考慮し20Fr以上の太いドレーンを使用することが望ましい．

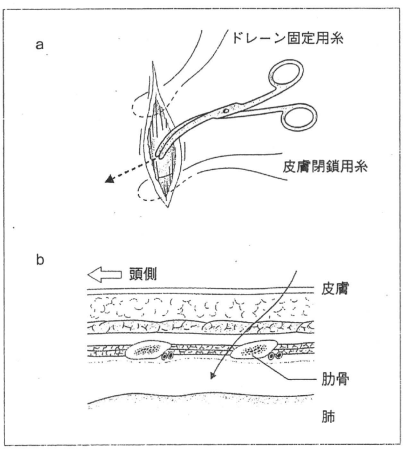
2 手技の実際

仰臥位または半側臥位にて患側上肢を挙上し，腋窩部がよく見えるような体勢にて手技を行う(図3)．ドレーン挿入にあたって，前腋窩線上第3～4肋間あたりの挿入予定部にマーキングするが，腋窩の有毛部にはドレーンは挿入しないようにする．皮膚消毒を行ったのち局所麻酔を行うが，特に痛みを感じやすい皮膚，骨膜，壁側胸膜の3箇所を重点的に麻酔する．特に壁側胸膜部分は痛みが強いため，十分麻酔しておく．

ドレーンを挿入する際には，まず挿入予定肋間より1肋骨分くらい尾側の皮膚を約1cm程度切開し，ドレーン固定用の糸とドレーン抜去時に創を閉じるための糸(筆者は2-0ナイロン糸)をかけたら，鉗子にて皮下組織ならびに肋間筋を剝離し，肋骨上縁で胸膜を破って胸腔に至る(**図4**)．その後，鉗子で作成したルートに沿ってトロッカードレーンを胸腔内に挿入する．ドレーン先端が胸腔内に確実に入るまではドレーンは内筒を入れたまま皮膚に垂直に近い角度で挿入し，胸腔内に数cm以上入った時点で上方に向きを変えて挿入していく(**図5a**)．最初から上方に向けて挿入すると，特に上部肋間では胸腔内に入らずに胸郭外を這って進んでいくことがあり要注意である(**図5b**)．



[図3] 腋窩から肺尖部へのドレーン挿入法
仰臥位にて患側上肢を挙上し，腋窩部の大胸筋外側縁後方第3～4肋間あたりからドレーンを挿入する．



[図4] 皮膚切開および胸腔への到達経路
挿入予定肋間より1肋骨分尾側の皮膚を1cm切開しドレーン固定用の糸と抜去時に創を閉じるための糸をかけ(a)，鉗子にて皮下組織ならびに肋間筋を剝離し，肋骨上縁で胸膜を破って胸腔に至る(b)．

3. 胸水のドレナージ法

1 考え方

胸水を有効にドレナージするためにはドレーン先端は胸郭背側，下部傍椎体付近に留置する必要がある(**図1b**)．

すなわち側臥位にて手技を行う．まずエコーにて後腋窩線上付近で胸水が貯留している場所を探す．横隔膜より少し上のレベルの肋間からトロッカードレーンを挿入する．立位では胸腔で最も低い場所は横隔膜上で，仰臥位では傍椎体部であるから(**図6**)，ドレーン先端部は横隔膜より少し上のレベルで傍椎体部に誘導することが望ましい(図1b)．ただし，術後症例など癒着が予想される場合には，胸部CTで胸水の局在を確認してお

◎air を有効にドレナージするためにはドレーン先端はできるだけ胸腔の前方を通って肺尖部に留置する．
◎胸水を有効にドレナージするためにはドレーン先端部は横隔膜より少し上のレベルで背側の傍椎体部に留置する．
◎ドレーンは先端が胸腔内に確実に入るまでは皮膚に垂直に近い角度で挿入して胸郭外への誤挿入を防ぐ．

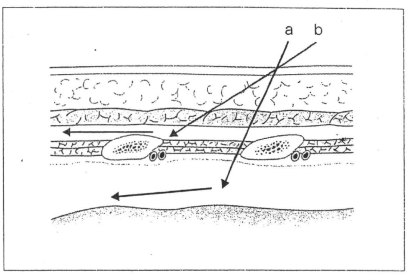
く必要がある．

排液が目的の場合，凝結塊やフィブリンでチューブが閉塞しやすいため，気胸の場合とは違って太さ 20Fr 以上のチューブを原則として使用する．悪性胸水であることが予想される場合には，後日胸膜癒着剤を注入する必要があるためダブルルーメンチューブを挿入しておいた方が便利である．また膿胸の場合にも無痩性膿胸である場合には，直ちに胸腔洗浄が必要なためダブルルーメンチューブを挿入する．

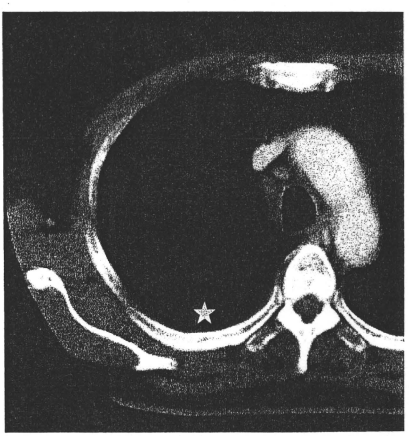
2 手技

基本的な手技は気胸の場合と同様である．違う点は挿入の方向であり，前述のように後腋窩線上から後方に向かって挿入する．ここでも胸郭外挿入にならないように注意する．左側では大動脈の損傷にも気をつける．また，ドレーンが葉間に入るとドレーンが利かないばかりか肺動脈の損傷の危険もあるため注意が必要である．

なお，術後患者のように胸腔内に癒着が予想される場合には，誤って肺内ドレーンにならないように皮膚切開を大きめに置いたうえで，指で探りながら胸腔を探し当てる必要がある．特に肺気腫の強い患者の場合には肺内にいったんドレーンが入ると，抵抗なく肺内をドレーンが進んでいくことがあり要注意である．CT 所見にて癒着などにより胸水や膿がドレナージの困難な場所に限局している場合には，肺を損傷せずかつ有効なドレナージを行うためにCT ガイド下で挿入することも考慮すべきである．



[図5] ドレーン挿入角度
ドレーンは先端が胸腔内に確実に入るまでは内筒を入れたまま皮膚に垂直に近い角度で挿入し胸腔内に数 cm 以上入った時点で上方に向きを変えて挿入していく（a：矢印）．最初から上方に向けて挿入すると胸郭外を這って進んでいくことがある（b：矢印）．



[図6] 排液用ドレーンの先端位置
胸腔内で仰臥位における最も低い位置は背側の傍椎体部であるから，排液用のドレーン先端はできるだけ横隔膜上方のこの位置まで誘導する（★）．

呼吸器外科

Knack & Pitfalls

専門医のための呼吸器外科の要点と盲点

【I】

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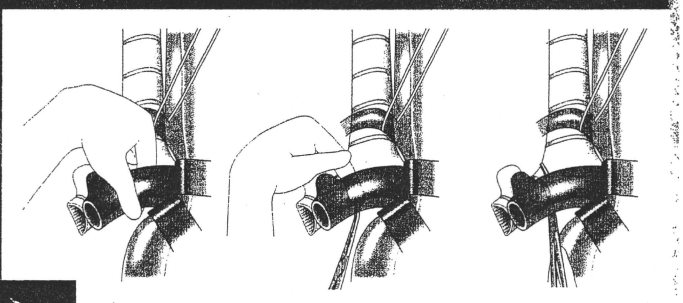

10）心嚢ドレナージ

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1. 心嚢液貯留の原因

心嚢液の貯留する原因はさまざまであるが，呼吸器外科領域では，肺癌患者において縦隔に進展した腫瘍が心膜に直接浸潤したり，転移したリンパ節が心膜に浸潤するなどして悪性心嚢液の貯留を引き起こし心タンポナーデを生じることはよく経験する．その他，乳癌など他臓器癌の心膜転移や縦隔リンパ節転移に伴う悪性心嚢液貯留や，胸部食道癌が心膜に浸潤，穿破して起こる化膿性心嚢液貯留，胸部食道癌に対する放射線治療後の晩期合併症としての反応性心嚢液貯留などもしばしば経験する．

2. 心嚢ドレナージの方法とそれぞれの適応

心嚢ドレナージの一般的方法としては，① エコーガイド下に穿刺してドレーンを挿入する方法，② 胸腔側よりアプローチして胸腔鏡下に心膜を大きく開窓し，心嚢液を胸腔内に流出させる方法，③ 局所麻酔下に剣状突起部直上を切開して直視下に心膜を切開しドレーンを挿入する方法（subxyphoid approach），がある．

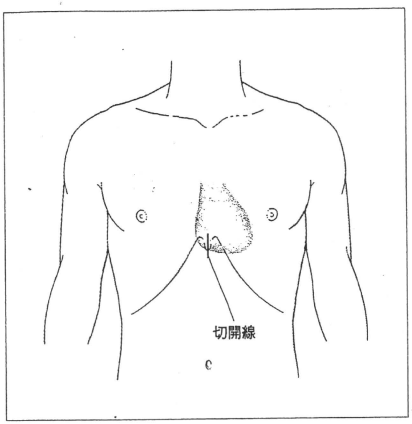
①の穿刺法は超音波装置の滅菌プローブさえあれば病棟でも簡便に施行可能であるという利点があるが，穿刺やガイドワイヤ挿入の際に心筋や冠動脈を損傷する危険性がある．また，細いドレナージチューブしか留置できないため，特に悪性腫瘍でよくみられる血性心嚢液の場合には，チューブが凝血塊で詰まりやすいという欠点がある．

②の胸腔アプローチによる心膜開窓法は，ドレーンの留置が必要ない点が長所であるが，全身麻酔と片肺分離換気が必要であり，全身状態の悪い患者や低肺機能患者にはリスクになることや，鏡視下に心膜を大きく開窓していく操作の際に心筋を損傷することがある，などの短所がある．また，悪性心嚢液の場合には胸腔に悪性細胞を流出させることにもなる．

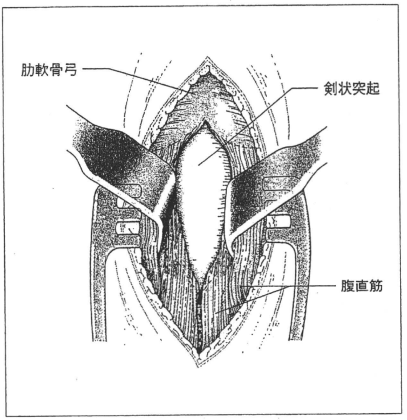
③の局所麻酔下での心嚢切開，ドレナージチューブ留置法は，太いチューブを留置できるため，血性の悪性心嚢液であっても凝血塊で詰まりにくく，またチューブに陰圧をかけることで癒着を形成し，将来心嚢液の再貯留を起こしにくい，癒着させるための薬液を後日心嚢に注入することも容易である，などの利点がある．しかも本手技は局所麻酔下で施行可能であり，また超音波プローブで確認しながら心膜を直視下に切開でき安全確実な手技である．次項ではこの③の手技を解説する．

3. 体位と準備

一連の手技は半座位にて行う．仰臥位に比べて，心嚢液が下方に貯留するため剣状突起下からのアプローチがより容易になる．まず体表面エコーを用いてあらかじめ横隔膜および心嚢の位置を確認し，皮切の適切な位置を決定しておく．心電図，血圧計，酸素飽和度のモニターと酸素投与は必ず行う．術中に心嚢を術野で確認するために使用する滅菌したエコープローブ（ペンシル型が



[図1] 心嚢ドレナージ時の皮膚切開
体表面エコーにて横隔膜および心嚢の位置を確認し，剣状突起部に4～5cm程度の縦切開を置く．



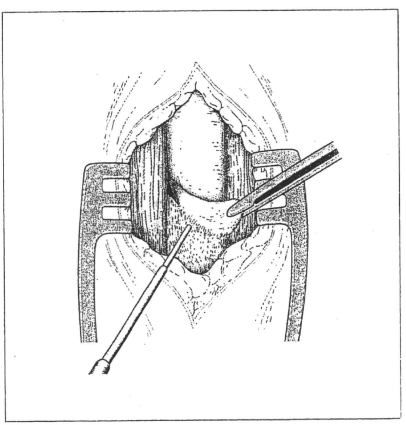
[図2] 剣状突起の露出
皮下組織を切開したら左右腹直筋を開排し，剣状突起を露出していく．

使いやすい）を必ず準備しておく．

4. 手術手技

十分な局所麻酔を行った後，剣状突起部直上に4～5cm程度の縦切開を置く（図1）．皮下組織を切開したら左右腹直筋間の白線（linea alba）を切開して腹直筋を開排し，剣状突起を露出していく（図2）．まず剣状突起表面および周囲組織を剝離したのち，剣状突起先端を把持して持ち上げ，裏面組織も剝離した後，剣状突起をリュール鉗子などを用いて切除する（図3）．これら操作の際の出血は電気メスでコントロール可能である．

続いて線維三角と呼ばれる膜様構造が現れるので，これを切開したら心膜脂肪組織が見えてくるので，これを剝離して心膜を露出する．心膜は光沢のある白色調の膜であり，慣れてくればすぐにそれと認識できるが，心膜に切開を入れる前にペンシル型エコーを当てて直下に心嚢液が見えるかどうか，また心臓の癒着が近傍にないかなどを全例必ず確認する．特に再手術例については細心の注意を払わないと，ドレーン挿入時に心筋を損傷し重大な事態を招く可能性がある．

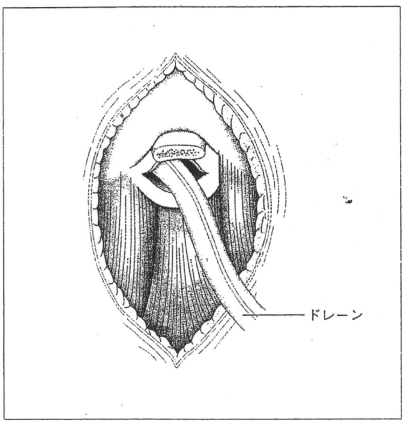


[図3] 剣状突起の剝離，切除
剣状突起表面，裏面の組織を剝離したのち剣状突起をリュール鉗子などを用いて切除する．

術野の心エコーにて直下に十分な心嚢液が存在することが確認できたら，心膜に切開を入れる．心膜を把持し挙上してから切開を入れることが望ましいが，実際には大量の心嚢液で心膜が緊満し

◎悪性腫瘍などによる血性心嚢液貯留の場合には太いチューブが直視下に留置できる subxyphoid approach が有用である.
◎心膜を切開する前に術野エコーで直下の心嚢液を確認し心筋損傷を予防する.
◎ドレーンは創から 3cm 以上皮下を這わせて体外に誘導し心嚢への逆行性感染を防ぐ.

把持できない場合も多く，その場合には直接メスで切開を入れる．心膜をわずかに切開しただけで直ちに心嚢貯留液が噴出してくるため，心嚢のすぐ外で吸引を続ける．一部を細胞診や培養検査に提出する．勢いが治まってきたら心膜切開縁を鉗子で把持し，鋏で切開をさらに広げた後，心嚢ドレーンを留置する（図4）．ドレーンは柔らかいものを用い，横隔膜上を沿うようにして背側に向け挿入していく．体表から心嚢への逆行性感染を防ぐため，ドレーンは創から直接出さずに，創から3cm 以上離れた部位まで皮下を這わせ，そこから体外に誘導する（図5）．心嚢内の感染は致命的であるので感染には注意したい．ドレーンを皮膚に固定したのち，腹直筋を密に縫合し，さらに皮膚縫合を行って閉創し手技を終了する．

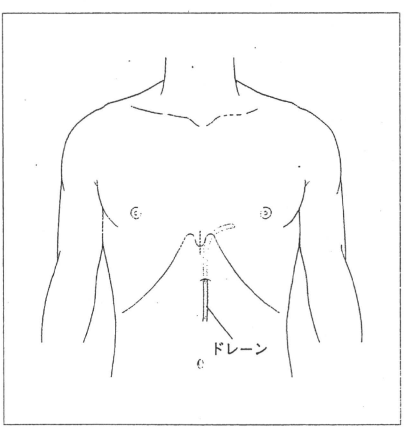


[図4] 心嚢ドレーンの留置
術野のベンシル型エコーにて直下の心嚢液を確認したのち鋏またはメスにて心膜に切開を入れドレーンを留置する.

5. 術後管理

術後はX線写真を撮影してドレーンの位置や気胸の有無を確認する．心嚢内上方に air が認められることがあるが（pneumoperitoneum），これは手技に伴うものであり，時間が経つと自然に消失する．局所麻酔下の手術であるから，経口摂取や歩行は当日内に可能である．

ドレーンは持続吸引を行う．4～5日間続けると自然に心膜が癒着し心嚢液が著明に減少し，抜去可能となる．抜去の目安は1日 30m*l* 以下である．大量の排液が持続するときには癒着させるための薬液を注入することもある．



[図5] 心嚢ドレナージ終了後
逆行性感染防止のためドレーンは創から直接出さずに3cm以上離れた部位まで皮下を這わせ体外に誘導する.

4 Total Mesorectal Excision and Lateral Pelvic Lymph Node Dissection

Miranda Kusters, Yoshihiro Moriya, Harm J.T. Rutten, and Cornelis J.H. van de Velde

TOTAL MESORECTAL EXCISION

Introduction

For rectal cancer, surgery is the principal treatment for cure. The main goal of surgical treatment is en bloc excision of the primary tumor with its locoregional lymph nodes. Furthermore, the focus of surgery is not only radical resection of the distal margin, but even more importantly at the circumferential margin. If the rectum is not removed within its envelope of mesorectal fascia, a subtotal resection with persistence of tumor cells and subsequent high chance for local recurrence is likely to occur.

In preoperative preparation, two aspects are essential in deciding whether, and which surgery, should be performed. First, the extent of spread of the tumor both locally and systemically needs to be established. This is achieved by physical examination, endoscopy, and preoperative imaging. Ideally, patients with rectal cancer are evaluated and discussed in a multidisciplinary setting and decisions as to whether neoadjuvant (chemo)radiation therapy can be made, especially in the setting of possible circumferential resection margin (CRM) involvement and/or nodal status. Tumors invading surrounding structures require en bloc resection with the primary tumor in order to prevent tumor spill. In unresectable, obstructive disease, palliative surgery may be required in the form of stoma construction.

Second is the evaluation of the fitness of the patient, as elderly patients often present with comorbidities, predisposing them to a higher likelihood of perioperative complications and associated higher risk of perioperative mortality. Postoperative mortality is at least

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double in elderly patients following resection compared to their younger counterparts (*1*). Further, in addition to oncological outcomes, postoperative quality of life is an objective in clinical decision making. Thus, good physical and mental condition is a prerequisite for major surgery.

History

The surgical treatment of rectal cancer has undergone significant evolution over several centuries. In the eighteenth century, the only resolution of obstructing colorectal cancer was a diverting colostomy. The first successful perineal excision of the rectum was performed by Lisfranc from Paris in 1826, (*2*) although the long-term results were poor. Czerny from Heidelberg first used a combined abdominal and anal approach in 1879, (*3*) because the tumor was too large for a perineal-only approach. By 1908, this combined abdominoperineal approach was perfected by Miles, through which curative surgery of rectal cancer became reality. Miles is to be credited for having introduced rectal cancer surgery based on the primary zones of lymphatic spread (*4*). The initial operative mortality rate was 42%, although the principles of resection of the zone of upward spread and a wide perineal approach are still important in rectal surgery today. In 1939, Lloyd-Davies (*5*) performed an abdominoperineal resection in which two surgeons operated simultaneously; one on the abdominal side, while the other performed the perineal phase of the resection.

While the abdominoperineal approach was performed for low lying rectal tumors, a solely abdominal approach was used for upper rectal cancer by Hartmann in 1921 (*6*). However, restoration of continuity of the colostomy was not an objective of this procedure. In 1939, Dixon (*7*) described a primary anastomosis after anterior resection. He believed that the distal margins had to be at least 5 cm in order to completely resect intramural disease spread and that the anastomosis had to be at least 6 cm from the anal verge to maintain continence. Thus, in the first half of the twentieth century, anterior resections were only performed in sigmoid lesions and the majority of rectal surgery was through an abdominoperineal approach. When pathologic studies demonstrated that there was generally a maximum of 2 cm of intramural disease spread and the construction of a low anastomosis became technically feasible through the introduction of mechanical staplers, the anterior resection began to gradually replace the abdominoperineal approach in mid-rectal tumors during the second half of the twentieth century. However, recurrence rates following low anterior resection were disappointing. Locoregional recurrence was reported to be between 25 and 50% after "curative" surgery.

The term total mesorectal excision (TME) was first introduced in a report by Heald in 1982 (*8*). He described the "holy plane," an avascular interface between the mesorectal fascia and the parietal dorsolateral pelvic fascia. He also stated that the rectum and mesorectum are an embryologically distinct lymphovascular entity. In TME surgery, dissection is along this "holy plane" through sharp dissection, in contrast to the more conventional blunt approach. Heald reported local recurrence rates well below 10% and survival rates of up to 87%.

The pathological basis of lateral tumor spread in the mesorectum was detailed by Quirke in 1986 (*9*). In contrast to routine sampling methods in which blocks are taken only from the distal surface, he developed a method in which tumor and mesorectum were sliced in the transverse plane. On an early analysis, the lateral resection margin involvement by tumor was present in 14 of 52 curatively operated patients, of which 85% developed local recurrence as a result of incomplete surgical resection. Quirke advocated that a TME might improve the results of the anterior resection.

Nowadays, the principle of TME has been accepted worldwide. An additional advantage of TME surgery is the excellent exposure of the pelvic floor and relative ease with which the surgeon is able to perform an anastomosis at this level. This fact has resulted in a steady decrease in rates of abdominoperineal resection in parallel to the increasing implementation of TME surgery.

Anatomical Considerations

The pelvis can be divided into two distinct anatomical compartments: the visceral and the parietal. The rectum and the anterior organs are the visceral organs, enveloped in the visceral fascia. The rectum is surrounded by a layer of fatty tissue, which contains lymph nodes and the superior and middle rectal vessels. The parietal compartment is the muscular and bony pelvic wall, covered by the parietal fascia.

Posterior to the rectum, the visceral and parietal fascia are separated by a layer of loose connective tissue. At the level of the third or fourth sacral vertebrae, a double layer of visceral fascia is present, the rectosacral fascia, which is firmly attached to the parietal fascia on the sacrum.

Anteriorly, between the visceral fascia covering the mesorectum and the seminal vessels and prostate in males, or the vagina in females, is Denonvilliers' fascia. More cranially, the peritoneum covering the pelvic organs reaches its deepest fold at the peritoneal reflection.

Laterally, the visceral fascia is attached to the pelvic side wall in the upper rectum. At the level of the mid-rectum, the attachment consists of thicker connective tissue, often referred to as the lateral ligament. This ligament contains the relatively small middle rectal vessels, lymphatic tissue and neurologic structures.

The pelvic nervous system is an intricate network of sympathetic and parasympathetic nerves (Fig. 1) (*10*). The preaortic hypogastric plexus originates from ventral roots of T12 through L2. These sympathetic fibers extend downward to the sacral promontory behind the pelvic fascia, where they divide into two hypogastric nerves. The parasympathetic nerves originate from the roots of S2–S4, which enter the pelvis through the sacral foramina. Laterally, the hypogastric nerves blend with these sacral nerves to form the inferior hypogastric plexus. This plexus lies in close proximity to the lateral part of the mesorectum. At this level, some branches of the plexus penetrate the mesorectal fascia for innervation of the rectum. The majority of the hypogastric plexus branches travel more anteriorly to innervate the urogenitary organs.

Technique

After a midline incision and retraction of the omentum and small intestine, the peritoneum is opened to the left of the sigmoid. The sigmoid is mobilized in an avascular plane between the mesocolon and the retroperitoneal fascia. The ureter and the ovarian (or spermatic) vessels lie just below this fascia. At the level of the sigmoid artery distal to the left colic branch, the superior rectal artery can be ligated and divided. In case of a high tie of the inferior mesenteric artery, it is important to identify the superior hypogastric plexus. Damage to this plexus might result in ejaculation disorders and urinary incontinence. The mesenteric vein can be ligated at the level of the artery. However, a tie just inferior to the pancreatic border enables maximal mobilization of the left colon, which may facilitate a low anastomosis in a later stage of the procedure. The mesosigmoid is divided and the sigmoid colon or distal colon is transsected with a considerable proximal margin from the tumor, at a level where good vascular supply is guaranteed.

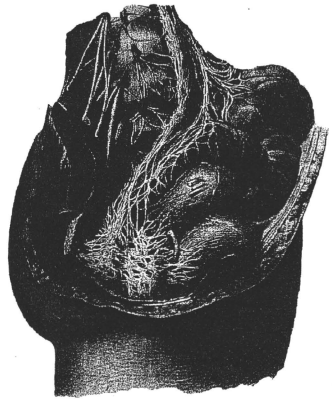

Fig. 1. Anatomic drawing of autonomic nervous system in a female pelvis *(10)*.

In the phase that follows, an undisturbed view and adequate lightning is essential. As the rectosigmoid is lifted anteriorly, the plane between the visceral and parietal fascia is identified. The presacral plane is opened sharply by diathermy or scissors. At the lateral side, the hypogastric nerves can be identified. Extending downward, the fascia on the piriform muscle, which is continuous with the rectosacral fascia, is uncovered. At the inferior margin of the piriform muscle, the pelvic splanchnic nerves are located. By meticulous sharp cuts of the parietal fascia, the roots of these nerves are exposed.

Subsequently, the rectosigmoid is moved posteriorly and the peritoneum is incised just anterior to the peritoneal reflection. Continuing the dissection between the rectum and the seminal vesicles or the posterior vaginal wall, Denonvilliers' fascia is identified. It serves as the reference plane, on which sharp dissection is carried downward and laterally. At the lateral edges of Denonvilliers' fascia the inferior hypogastric plexus divides into branches to the rectum (lateral ligament) and the genitourinary organs. By pushing the rectum contralaterally and dorsally, the branch to the rectum can easily be divided. Electrocautery should not be used to avoid damage to the inferior hypogastric plexus. Denonvilliers' fascia ends distal to the prostate in males and proximal to the perineal body in females. At this level, further dissection is possible only in the thin ventral mesorectum. After transsection of the lateral ligament, the lateral mesorectum can be followed down to the pelvic floor.

Then, the rectum is only attached to the pelvic floor. Dependent on tumor location, the next step is either the perineal phase in the case of an abdominoperineal resection, or cross-clamping, washing out, dividing and stapling of the rectum in the case of a low anterior resection.

Nerve-Sparing Surgery

Deliberate tracking and preservation of the autonomic nerves combined with TME was introduced in Western countries and performed in 246 patients with Dukes B or C rectal cancer by Enker, beginning in 1991 *(11)*. The 5-year local recurrence and survival rates were 7.3 and 74.2%, respectively. Functional results in a group of 136 patients showed that 73% of the males and 64% of the females had no urinary complaints. In male patients, sexual function was related to age and to the type of surgery. All 33 patients who were younger than 60 years and who underwent low anterior resection maintained erection and sexual function. After APR and in older patients, however, spontaneous erection was diminished in 19–29% and ejaculation disturbed in two-thirds of the patients. In female patients, 86% of sexually active patients remained sexually active after the operation *(12)*. Since these reports, functional results have been further studied extensively.

Urinary Function

The sympathetic nervous system plays a major role in urinary continence, while the parasympathetic nervous system is essential for normal voiding *(13)*. Symptoms associated with injury include difficulty in bladder emptying, overflow incontinence, and loss of sensation of bladder fullness. However, it is still unclear exactly what injury and to which autonomic nerves or plexuses causes urinary dysfunction.

Currently, the incidence of urinary dysfunction after TME surgery varies between 30 and 70% *(14–17)*. In the Dutch TME trial, in which 785 patients were questioned about urinary function, incontinence was reported in 38% of patients and voiding difficulties in 31% *(18)*. Preoperative incontinence and female gender were risk factors for incontinence, while preoperative voiding dysfunction, intraoperative blood loss, and autonomic nerve damage were associated with voiding difficulties.

Thus, damage to the autonomic nerves during surgery is still a major problem. Adequate autonomic nerve identification is influenced by patient gender, the learning curve of the surgeon, and T-stage *(15)*. Intraoperative blood loss and obesity also make identification difficult, and nerve sparing virtually impossible *(18,19)*.

Causes of urinary dysfunction other than pelvic nerve damage have also been identified. Previous hysterectomy in females and posterior tilting of the bladder during an abdominoperineal resection may weaken the pelvic floor, aggravating incontinence *(20)*. Further, surgical interruption of the levator ani muscle innervation during abdominoperineal surgery may result in loss of support of the bladder, which can be associated with incontinence *(21)*. Radiotherapy seems to have less influence on urinary function.

Sexual Function

Sacrifice of the superior hypogastric plexus in males is associated with ejaculation dysfunction. Impotence is probably the result of damage to the inferior hypogastric plexus *(13)*. In females the sympathetic nerves are considered responsible for the rhythmic contraction of the genital ducts and organs during an orgasm. The parasympathetic nerves are associated with increased blood flow to the vagina and vulva, causing vaginal lubrication and swelling of the labia and the clitoris *(22)*. However, reports on sexual function in women are scarce and many aspects are still unknown.

The largest study published about autonomic nerve preservation with TME is the Dutch TME trial. Four hundred ninety-three patients received no neoadjuvant therapy. Before treatment 78% male patients and 50% of female patients were sexually active. Two years after surgery, 76% of the males who were previously active were still active; for females this was 90%. In males, erection and ejaculation disorders occurred in 47 and 32%, respectively.

Vaginal dryness occurred in 35% of the females and pain during intercourse was present in 20%. Radiotherapy had a negative influence on sexual activity and functioning *(23)*.

Therefore, even after preservation of the autonomic nerves, sexual functioning frequently declines after TME surgery. As most patients are older, one factor of influence might be a physiological decline in sexual function, as well as a higher prevalence of cardiovascular disease with associated medications that may impact sexual functioning *(24)*. Further, nerve preservation is more difficult during APR-surgery compared to low anterior resection, as determination of the correct surgical plane and visibility in the perineal phase is challenging. In addition, as the results of the TME trial show, the addition of radiotherapy influences sexual functioning considerably *(23)*. A short- or long course of radiotherapy is the standard neoadjuvant treatment in most Western countries, adding further morbidity.

Defecation Function

Normal defecation function is dependent on adequate defecation reflexes, which are an interaction between reservoir and sphincteric functions. Sphincter-saving surgery has become increasingly common since the introduction of stapling devices and better assessment of the extent of intramural tumor growth. However, a portion of the patients having undergone a low anterior resection suffer from defecation dysfunction, such as soiling, incontinence, and urgency. This is referred to as the low anterior syndrome.

Incontinence is reported to be present in 20–40% of patients undergoing sphincter-saving procedures *(25,26)*. The exact mechanism of incontinence is unknown, but poor functional outcomes are associated with low anastomoses or anastomotic leakage *(27)*. Lower anastomoses may cause more injury to structures in the sphincter complex, causing a deterioration of reservoir function and loss of the defecation reflex. To improve continence in very low anterior resection, the construction of a colonic J-pouch has been suggested *(28)*. Reduction of capacity of the neorectum following an anastomotic leak might underlie the increased incidence of defecation dysfunction *(29)*. Radiotherapy also has been described as reducing fecal continence, causing incontinence in 50–60% of patients *(23,25–27)*. The anal function is probably maintained after radiotherapy, although rectal compliance might be compromised *(27)*. The avoidance of a permanent stoma by sphincter-saving surgery is generally seen as the best strategy. However, patients having undergone an abdominoperineal resection have been reported to have fewer physical and psychological difficulties compared to patients undergoing low anterior resection *(23)*.

Besides the role of parasymphathetic and symphathetic nerve supply in fecal and urinary continence, recently the role of a previously neglected nerve, the levator ani nerve, has been described *(30)*. Common knowledge is that the pudendal nerve innervates the levator ani muscle, but the levator ani nerve is a separate nerve, which arises from the sacral nerves S3 and/or S4. It lies in the field of TME surgery and can be disrupted during the operation, when the parietal fascia is accidentally entered during posterior dissection. The risk of levator ani nerve disruption is substantial, especially in low lying tumors, which could contribute to an increased risk of urinary and fecal incontinence. Adhering to the surgical plane, refraining from blunt dissection and improving rectal traction may lower the risk of levator ani nerve disruption *(30)*.

Anastomotic Leakage

Anastomotic leakage is one of the most serious and potentially life-threatening complications in colorectal surgery. Since the introduction of TME the risk for symptomatic anastomotic leakage has increased *(31)*. This can probably be explained by the increase in sphincter-saving procedures and subsequent lower anastomoses since the introduction of TME.

Other explanations might be compromised blood supply to the remaining rectum by TME and accumulation of hematoma in the large pelvic space after removal of the mesorectum, leading to pelvic sepsis *(32)*.

Currently the incidence of anastomotic leakage in patients undergoing a low anterior resection with the TME technique is around 10–18% *(32–35)*. However, comparison of studies is difficult due to a lack of standardized definitions. Anastomotic leakage may present as generalized peritonitis requiring abdominal reoperation; however, pelvic abscesses, discharge of pus per rectum or a rectovaginal fistula are defined as anastomotic leakage in some reports. Sometimes a subclinical leak is only incidentally detected on contrasted radiographic studies. This wide spectrum of presentations of anastomotic leakage thus not only makes it difficult to accurately report the incidence, but also hinders adequate detection of this life-threatening condition in individual cases.

In retrospective studies with uni- and multivariate analysis, several risk factors are associated with anastomotic leakage in rectal cancer. There is common agreement that male gender and low anastomoses are important risk factors *(34,36)*. Other technical factors have been reported as factors of influence, including bowel preparation, pelvic haemostasis, anastomotic tension, complete doughnuts, and intraoperative testing of the anastomosis *(34)*. Whether the operation was performed in an emergency setting and whether the anastomosis was hand-sewn or stapled also seems to affect the incidence of anastomotic leakage *(37,38)*. In the Dutch TME trial the absence of pelvic drainage and the absence of a covering stoma were associated with an anastomotic leakage *(32)*. Lastly, preoperative radiotherapy is mentioned as a predisposing factor in some studies, *(35,39–41)* while this was not found in large randomized studies *(42–44)*.

The 30-day postoperative mortality rate after anastomotic leakage is generally between 10 and 20% *(32,33,45,46)*. However, even if postoperative deaths are excluded, patients with an anastomotic leak have a poorer prognosis. Anastomotic leakage is even reported to be associated with oncologic outcomes following rectal cancer surgery. Local recurrence rates are higher in patients with anastomotic leakage, *(33,46,47)* although this is not confirmed in all studies *(48)*. There are a few theories explaining the mechanisms by which anastomotic leakage may adversely affect oncologic results. First, there is some evidence that local tumor recurrence after anastomotic leakage can be caused by a "wash-out" of exfoliated tumor cells from the bowel lumen into the wound cavity, *(49,50)* resulting in disease upstaging and reducing survival. Secondly, the inflammatory response to anastomotic leakage might play a role. The release of proinflammatory cytokines and growth factors as part of the systemic inflammatory response secondary to intra-abdominal sepsis, and the associated immunosuppression, may have a direct effect on the growth of residual tumor cells *(51,52)*. Thirdly, there is a possibility that leaks occur as a consequence of other conditions, which themselves lead to local recurrence and reduced survival. We recently speculated that transit tumor cells from the lateral lymph nodes might "leak" back into the surgical wound after TME, causing local recurrence *(53)*. This tumor containing lymph fluid, collected presacrally in a seroma, could induce an inflammatory reaction which also affects the anastomosis. This theory would suggest that anastomotic leakage is not affecting tumor progression, but that tumor cells themselves indirectly cause anastomotic leakage and local recurrence. This theory remains speculative and requires further study.

Independent of what the cause of anastomotic leakage is, the best approach is prevention. Of the aforementioned risk factors, some cannot be prevented, but the specific technical factors can be influenced. Special staplers might also strengthen the anastomosis and by early identification of symptoms of anastomotic leakage, emergency situations might be prevented. Further, a construction of a diverting stoma decreases the rate of symptomatic anastomotic leakage *(35,48)*. As the fecal stream is diverted, the anastomosis can heal appropriately,

although restoration of intestinal continuity by a second operation with associated morbidity and mortality must be considered. Further, it is unknown whether diversion reduces local recurrence or improves survival. Thus it can be concluded that anastomotic leakage is a severe complication of rectal surgery whose pathophysiologic mechanism remains unknown.

Possible Causes of Local Recurrence: The Dutch TME Trial

The TME trial is a large prospective randomized multicenter study in which 1,861 patients (of which 1,530 were Dutch), were enrolled between January 1996 and December 1999. This trial analyzed the effect of short-term preoperative radiotherapy (5×5 Gy) in patients operated with a TME (RT+TME), compared to patients with TME alone (TME) *(43)*. Inclusion criteria were the presence of a primary adenocarcinoma of the rectum, without evidence of metastatic disease at the time of surgery and tumor location within 15 cm from the anal verge. Patients with other malignant diseases or with fixed tumors were excluded. Standardized techniques for surgery, radiotherapy, and pathology were used *(54)*.

The 5-year local recurrence rate of patients having undergone a macroscopically complete resection was 5.6% in case of preoperative radiotherapy, compared with 10.9% in patients undergoing TME alone ($p<0.001$). Overall survival at 5 years was 64.2 and 63.5%, respectively ($p=0.902$). In multivariate analyses a significant effect of radiotherapy in reducing local recurrence risk for patients with nodal involvement, for patients with lesions between 5 and 10 cm from the anal verge, and for patients with uninvolved CRM was seen *(55)*.

In a recently conducted study, the patterns of local recurrence in the Dutch patients of the TME trial were analyzed in efforts to reconstruct the most likely mechanisms of local recurrence and the effect of preoperative radiotherapy *(56)*. All patients with a local recurrence, defined as any rectal cancer recurrence in the small pelvis, were identified. Available images of the primary tumor, the images at the time of discovery of the local recurrence and the prospective data were reviewed case by case by a team consisting of two radiologists, one radiation oncologist and one surgeon. Examining the images and data, the location of the recurrence was classified into one of the following subsites: presacral, anterior, anastomotic, lateral, or perineal. The results showed that at a median follow-up of 7.0 years, 114 of the 1417 patients developed a local recurrence; 36 patients in the RT+TME group (5-year 4.6% LR-rate) and 78 patients in the TME group (5-year 11.0% LR-rate).

The subsites of local recurrence are presented in Table 1. Presacral local recurrences occurred most in both randomisation groups (5-year local recurrence rate RT+TME: 2.0% and

Table 1
Subsites of local recurrence

	RT+TME N=713	*TME N=704*
Presacral	15 (2.0)	25 (3.6)
Lateral	9 (1.1)	14 (1.9)
Anterior	6 (0.7)	14 (1.9)
Anastomosis	5 (0.7)	19 (2.7)
Perineum	0 (0)	4 (0.6)
Unknown	1 (0.1)	2 (0.3)
Total	36 (4.6)	78 (11.0)

Values in parenthesis are 5-year LR-rates, by competing risks analysis

TME: 3.6%). There was a significant difference between the two randomisation arms in the anastomotic subsite, with 0.7% 5-year local recurrence in the RT+TME group and 2.7% in the TME group ($p = 0.003$). Lateral local recurrences comprised about 20% of all local recurrences.

Since this trial, preoperative imaging, preoperative therapy, surgery and adjuvant treatment modalities have changed; nonetheless, these new data give insight into the genesis of local recurrence and help in the understanding of how to prevent local relapse in current rectal cancer treatment.

Advanced Disease

In the Dutch TME trial, surgeons were trained in TME-surgery by workshops and tutorials in order to achieve optimal surgical quality. Although locally advanced tumors were supposed to be excluded, only fixed tumors at rectal examination could be identified, since routine imaging was not mandatory at that time *(43)*. However, histological evaluation of the circumferential resection margins (CRM) suggested that a substantial proportion of advanced tumors had been included *(57)*. In the TME trial CRM-positivity was 17% and even as much as 30% after an abdominoperineal resection. Our hypothesis is that this advanced disease is the main cause of the high rate of presacral local recurrences *(58)*.

An involved or close circumferential resection margin (CRM) has repeatedly been confirmed as one of the most important risk factors for local recurrence *(57)*. Apart from the CRM, T4 tumors and massive lymph node involvement (N2 disease), all signs of advanced disease, can currently be identified by preoperative MR imaging *(59,60)*. In the Dutch TME study, at least 30% of the tumors could be defined as advanced, in retrospect *(56)*. In most cases, a long course of neo-adjuvant (chemo)radiation, rather than a short-course of radiotherapy, can probably downstage these tumors and lead to better results *(61)*. Thus, nowadays, with good imaging and preoperative discussion in a multidisciplinary setting, a positive margin is probably more a sign of inadequate surgical technique rather than unrecognized advanced disease *(62)*.

Low Anterior Resection

In the TME trial, apart from presacral recurrences, anastomotic recurrences were relatively frequent, especially in non-irradiated LAR patients *(56)*. Most of the anastomotic recurrences following sphincter-saving surgery in limited disease could probably have been prevented by a longer distal margin. TME alone in node-positive tumors resulted in considerable local recurrence rates when distal margins were 2 cm or less. The addition of radiotherapy resulted in few local recurrences, except when distal margins were less than 5 mm.

This suggests that TME without radiotherapy in node-positive disease requires a longer distal margin than in node-negative disease. Without preoperative irradiation, a short distal margin of 1 cm can be accepted in node-negative patients, whereas in node-positive patients, a margin longer than 2 cm is required. Radiotherapy can prevent anastomotic recurrences, except when distal margins are < 5 mm. MRI techniques and lymph node specific contrast agents may allow reliable assessment of lymph node status in the near future, so that customized surgery can be applied according to preoperative staging *(60,63)*.

A complicating factor in analyzing the sphincter-saving procedures in the TME trial is that a total mesorectal excision down to the pelvic floor was not mandatory and surgeons were allowed to transect the mesorectum 5 cm below the tumor. Unfortunately, it is unclear what proportion of the patients received a partial mesorectal excision instead of a TME. It has been reported that distal mesorectal spread is documented in 10-15% of rectal cancer patients, usually within 2-3 cm of primary disease and more often in the form of small

mesorectal deposits than involved nodes *(64–66)*. Koh et al *(67)*, examining the distribution of mesorectal lymph nodes based on imaging and histopathology, found very few lymph nodes distal to the tumor. This in contrast to an anatomical cadaver study of Perez et al *(68)*, who found lymph nodes up to the distal third of the mesorectum.

Thus, data are conflicting, but surgeons should be aware that in node positive patients a transection of the mesorectum closer to the tumor carries a risk of leaving small tumor deposits behind. This should be kept in mind when, for whatever reason, a patient is not receiving preoperative radiotherapy. In these situations, a mesorectal transection of 5 cm below the tumor is a wise precaution.

Abdominoperineal Resection

APR-surgery has shown poor results in several reports, with higher local recurrence rates compared to low anterior resections *(69)*. In the TME trial, APR-surgery mainly resulted in presacral local recurrences *(56)*. It is known from previous studies that APR is associated with higher CRM involvement *(57)*. Anatomical and radiological studies show that in the lowest part of the rectum the mesorectum tapers and terminates at the pelvic floor *(70)*. If a tumor is located in the distal third of the rectum, the surrounding mesorectum is very thin, especially on the ventral side. Near the anal margin the visceral fascia (covering the mesorectum) blends with the parietal fascia (covering the levator ani muscle), forming the corrugator muscle, which separates the internal from the external sphincter. At this level a tumor that extends only a few millimeters beyond the muscular bowel wall is at risk for a positive margin when following the normal resection plane.

Even when negative margins are achieved, these low tumors seem to behave differently compared to proximal tumors. In studying the patterns of recurrence, as much as 18% of the CRM-negative N+ tumors operated by APR developed a local recurrence *(56)*. Apparently, in these low tumors, tumor particles still seem to be left behind, even when the circumferential margin seems sufficient, causing local recurrences at various subsites.

A wide APR, resecting the complete levator ani muscle, might provide better local control of low tumors *(58,72)*. Japanese surgeons advocate the lateral lymph node dissection (LLND), as distal tumors are known to metastasize to lateral lymph nodes, as discussed below. This can be combined with chemoradiation prior to surgery in low T3 tumors, as if they are true locally advanced disease *(73)*. This has been reported to result in downstaging and even the possibility of sphincter-saving surgery in some instances *(73)*.

Lateral Disease

Although the main lymphatic flow is upward in the mesorectum, involvement of lateral nodes outside the mesorectum does occur. In the TME trial lateral local recurrences represent about 20% of all local recurrences, a figure in accordance with an overview of Roels et al *(74)*. We can conclude that lateral disease is responsible for a considerable amount of local relapse. When analyzing only low rectal tumors, where lateral lymph node spread is especially present, the lateral recurrence rate in the nonirradiated TME group of the Dutch TME study was 2.7%, comprising 24% of all local recurrences. The difference in lateral recurrence in the RT+TME group (0.8%) vs. the TME group was significant, suggesting that radiotherapy plays a significant role in the reduction of local recurrence in the lateral pelvic subsite. Thus, radiotherapy can probably sterilize lateral tumor particles in most of the cases *(58)*.

A problem, however, arises if positive lateral lymph nodes are not included in the radiation target volume, as can occur where more accurate delineation of pertinent nodal basins are required (i.e. in intensity modulated radiation therapy (IMRT) planning). In contrast to the TME trial, in which the lateral lymph nodes were probably always irradiated, some nodal basins have the potential to be underirradiated or excluded with advanced radiation therapy planning techniques, emphasizing the importance of knowledge of patterns of spread and careful radiation planning when adopting these techniques.

The question remains, however, whether tumor cells in the lateral lymph flow routes are responsible for only lateral local recurrences, or whether they also result in recurrences in other pelvic subsites. Comparing the LLND in Japanese patients with TME in Dutch patients, the number of presacral local recurrences was higher in the Dutch group *(58)*. However, it is unclear whether this difference is caused by removal of the lateral lymph flow routes or by a wider APR practiced in Japan, resulting in less CRM involvement. We will discuss this subject further in the next section of this chapter.

Future Perspectives

The introduction of TME surgery in combination with neoadjuvant treatment has reduced the local recurrence rate considerably *(55,75)*. On a population level it seems that even survival of rectal cancer patients is steadily improving *(76)*. However, surgical treatment also carries a relative high morbidity rate *(18,23,77,78)*. It is probable that only a minority of patients benefit from the addition of neoadjuvant treatment. Improved preoperative evaluation will allow a more tailor-made approach. MRI has proven to be very accurate in visualizing the relation of the tumor with the mesorectal fascia *(60,79)*. Promising data have been published about the capability of identifying lymph node metastases with special contrast agents *(80)*. Furthermore, translational research will help to identify those patients with a high local recurrence risk and therefore benefiting from neoadjuvant treatment versus those at low risk *(81)*. It is to be expected that for the near future the quality of surgery *(71)* and the presence of lymph nodes *(82)* will remain important variables to base such a decision on. Appropriate staging of lymph nodes may open the door to more organ preserving treatments like proposed by Habr-Gama *(83)*. The best treatment for involved lymph nodes still remains uncertain: neoadjuvant treatment with its inherent toxicity or selected lymph node dissection of the lateral zones of spread. In the next part of this chapter, the role of the LLND will be explored.

LATERAL LYMPH NODE DISSECTION

From anatomic studies it has been shown that lymph node drainage occurs retrograde along the arterial vessels of the rectum. The complex network of lymphatic channels can be divided into three lymphatic flow routes. The upper route is along the superior rectal artery in the direction of the inferior mesenteric artery. The lateral route reaches from the middle rectal artery to the internal iliac and obturator basins. And the third, downward, route extends to the inguinal lymph nodes. The downward route is only involved when tumor growth has infiltrated into the anterior organs. The upper route is enveloped in the mesorectum and is thus removed in standard TME. The lateral route has been shown to be involved, especially in low and more advanced rectal cancer.

History

The treatment of lymph node metastases in the lateral lymph flow route has been controversial and has undergone different development in the East and the West.

West

The division of the rectum in two main lymphatic zones has been known since 1895, when Gerota described these from anatomic studies *(84)*. Nevertheless, the description of Miles *(4)*, of solely up- and downward spread, was generally accepted. He stated that the zones of "lateral spread" were located between the levators ani and the pelvic fascia, thus promoting a wide abdominoperineal resection as the method to resect these lymphatic networks.

Results, however, differed between lower and higher rectal carcinomas, with 5-year survival rates between 25 and 45% in lesions up to 6 cm from the anal verge and 30–80% in lesions at least 6 cm from the anal verge *(85,86)*. This difference between high and low lesions was also apparent when lesions were treated by abdominoperineal resection alone, with a similar worse outcome in local recurrence rates between high and low lesions *(87)*. Meanwhile, the significance of the peritoneal reflection and the middle valve of Houston as a landmark in low and high lesions was described by Villemin and Oliveira *(88,89)*. According to these authors, this level was the border between two lymphatic areas of the rectum.

In 1940, Coller described that in 7 of 19 very low lying rectal cancers, there was nodal involvement up to the margin of the excision of the levator ani muscle *(90)*. Dukes suggested in 1943 that growth might be laterally along the lymphatics accompanying the middle rectal vessels *(91)*. Sauer et al *(92)* stated in 1951 that the "lateral spread" suggested by Miles was an anatomic misinterpretation. He quoted previous studies in which it was described that not all nodes are located over the levators ani, but rather on the pelvic walls and within the lateral ligaments. Lateral spread into these lateral lymph nodes would be responsible for the worse results seen in low rectal cancers as compared to higher disease. Waugh and Kirklin had a similar argument *(85)*. Sauer reported on 17 patients with low rectal carcinoma undergoing extended dissection of the iliac and sacral nodes, with two cases demonstrating metastases in the lateral nodes. In higher tumors, no lateral metastases were found. In later series he reported no increase in mortality or morbidity by LLND, although survival numbers were not given.

Stearns and Deddish *(93)* examined the role of abdominopelvic lymphadenectomy in the management of rectal cancer in 1959. One hundred twenty-two patients with high and low rectal carcinoma underwent resection, although lateral lymph node metastases occurred only in tumors located <10 cm from the anal verge. In Dukes C patients, the 5-year survival for the extended operation was 40%, while it was 23% in conventional surgery. Because this difference was not significant, and morbidity was significant, the authors suggested that LLND had no beneficial effect.

Enker et al *(94)* reported on LLND in 1986 in order to set objective definitions for LLND surgery. One hundred ninety-two of 412 patients underwent en bloc pelvic lymphadenectomy, mainly for low and middle rectal tumors, combined with abdominoperineal resection or low anterior resection. A difference with the method of Stears and Deddish was that obturator compartment remained undissected, only dissecting the para-iliac nodes. Enker observed a superior survival after extended dissections, when compared to conventional resections (63.8% vs. 54.3%) in Dukes C patients in particular. There was no added operative mortality and in terms of morbidity, only urinary function was mentioned as being temporarily compromised. Enker suggested LLND as appropriate therapy when preoperative examination suggests that the rectal cancer penetrates the bowel wall.

A group of patients having undergone LLND was retrospectively reviewed by Glass in 1985 *(95)*. Based upon vague indications, namely local extension or unfavorable histologic grade, 75 patients underwent LLND. These were compared to 2,266 patients who underwent conventional resection. No improvement in 5-year survival or local recurrence rate was observed in patients with the extended resection, thus the authors concluded that no patients would benefit from LLND.

In 1992, Michelassi reported on 73 patients who had conventional surgery and 64 who underwent wide pelvic lymphadenectomy *(96)*. The indications were dependent on the surgeons' preference. There was a reduction in local recurrence rate from 16.4% to 9.4%, but this was not significant. No numbers were given on survival or morbidity.

Following this, only few reports from Italy described outcomes of LLND in Western patients, as focus was more on TME and (neo)adjuvant regimens in the treatment of rectal cancer in the 1990s.

East

Reports on the LLND in the East mainly come from Japan. There, Senba *(97)* conducted a study of lymphatic system of the rectum in more than 200 fetuses. He found the same routes as Gerota in 1908, *(84)* but also found an additional route running along the inferior rectal artery, passing through the ischiorectal fossa, to the internal iliac artery.

In a report from 1940, Kuru *(98)* applied the knowledge of the lateral lymph flow route directly to the clinical setting. One hundred twenty-six patients underwent LLND; overall lymph node involvement was 42% and lateral lymph node involvement was approximately 9%. In low rectal cancer, lateral lymph node involvement was seen in 4 of 13 cases (31%). In 1977, Koyama reported a 5-year survival of 45% in LLND patients vs. 30% in conventional surgery *(99)*.

The first English report on LLND surgery performed from 1962 to 1976 was from Hojo *(100)*. He reported better survival rates following the introduction of LLND at the National Cancer Center Hospital (NCCH) in 1969 (5-year survival rates of 71% vs. 59%). Local recurrence rate was significantly reduced in Dukes B lesions (25% to 7%). Lateral lymph node positivity was observed in 20% of low rectal cancer vs. 6% in higher cancers. In 1989, Hojo reported on urinary dysfunction and sexual dysfunction, occurring in 39 and 76%, respectively, of LLND patients *(101)*. He concluded pelvic nerves should be preserved in patients with lower rectal cancer without lymph node spread.

In 1991, Sato described the results of anatomic dissections of 45 cadavers, in which he observed that the lateral ligament could be divided into a medial part, primarily containing the middle rectal artery, and a lateral part in which the pelvic plexus was located *(102)*. To reduce urinary and sexual dysfunction Hojo reported how injury to this plexus could be avoided through nerve-sparing techniques *(103)*. Moriya described several nerve-sparing techniques in 1995 *(104,105)*. Dependent on tumor extent, total or partial nerve preserving techniques were applied. In total nerve preservation, urinary function was preserved in 98% of the cases and erection was preserved in 90%, although ejaculation was possible in only 68%. Operative time was 90 min longer as compared to more limited operations. Oncologic outcomes did not seem to be compromised by autonomic preservation *(106)*.

In 1998, Mori *(107)* reported on 803 patients in which he found lateral lymph node metastases in 25.5% of 157 patients with Dukes C stage low rectal carcinoma. The mean 5-year survival rate of patients with lateral lymph node metastases was 37.5%. Sexual function was reported to be poor in unilateral autonomic nerve preservation. In bilateral preservation erection could be achieved in 75% and ejaculation in about 50%.

In 2005, Matsumoto *(108)* analyzed 387 lymph nodes after bilateral LLND and found that 15.5% of histologically negative lymph nodes were shown by RT-PCR to harbor micrometastases. The possible survival benefit of resection of micrometastases by LLND was described by Sugihara, *(109)* who reviewed 2,916 patients from various centers. Stage II disease patients undergoing LLND had a better (87.1%) 5-year survival relative to patients without LLND (78.0%). He concluded that these results may be due to resection of micrometastases by LLND, which would not be considered to be involved in standard histopathology.

West vs. East

Comparing data on LLND is difficult, not only because of nonrandomization and selection-bias, but also because of the following differences between the East and the West, which further hinder reliable comparison.

First, the definition of rectum and low rectal cancer differs between the continents. In the West, distance from the anal verge is often measured by rigid endoscopy and the rectum is mostly defined as 15–16 cm from the anal verge *(54,110)*. The distance of a rectal carcinoma from the anal verge is the distance between the lower edge of the tumor and the anal verge. The definition of low rectal carcinoma differs per publication, but mostly between 5–6 cm from the anus, as measured by endoscopy. In the East, in particular in Japan, definitions are related to anatomy rather than endoscopic measurement. The rectum is located below the lower border of the second sacral vertebral body and the rectosigmoid is located more proximal, up to the level of the promontory *(111)*. "Low" rectal cancer is defined as a tumor of which the major part is located at or below the peritoneal reflection, as seen on preoperative imaging or as palpated intraoperatively. Due to anatomic variations and differences in sex, the distance of the peritoneal reflection to the anal verge can differ from 6 to 9 cm *(112)*. Thus, cohorts of patients with low rectal carcinoma in Japan probably also contain tumors which would be defined as "middle" in Western terms.

Secondly, pathologic techniques differ between the East and the West. In the West, the resected specimen is first fixated and then sliced in order to perform CRM measurement according to the method of Quirke *(113)*. During this process, the number of resected lymph nodes are counted. In Japan, lymph nodes are harvested from the fresh specimen by the surgeons, directly after surgery *(111)*. This immediate harvesting of lymph nodes precludes assessment of the CRM at a later stage. Thus, the focus of pathology is on CRM-management in the West and lymph node harvesting in the East. The difference in average number of lymph nodes harvested might be a result of these differences in technique, as the number of mesorectal lymph nodes (without LLND) is generally at least 20 in Japan, rarely reaching that amount in the West. Further, removal of lymph nodes might be more difficult in Western patients, as only a low number of lymph nodes could be removed from Dutch patients by Japanese clearing methods in one series *(114)*. It is well known that removal of higher numbers of lymph nodes results in better staging, or maybe even upstaging, referred to as the Will-Rogers phenomenon *(115)*. This automatically changes prognostic outcomes and therefore can be responsible for differences between various groups.

Lastly, consideration of differences in body mass index is crucial in comparing the feasibility of LLND in Japanese and Western patients. Japanese patients, particularly males, are significantly thinner than Western patients *(116)*. Obesity makes LLND with nerve-sparing techniques considerably more difficult, which might result in more complications and morbidity. These might overshadow oncologic outcomes and worsen results of LLND in Western patients, as compared to Japanese patients.

Technique

When the rectum is removed via low anterior resection or abdominoperineal resection, TME is followed by LLND. As in the TME procedure, the inferior hypogastric plexuses have been identified and separated from the proper rectal fascia; in the lateral ligament, only the lateral part is left. The lateral dissection is started along the inner side of the internal iliac vessels and proceeds down to the stump of the middle rectal artery. The vessels are cleared of lymphatics and fatty tissue by sharp dissection using electrocautery, avoiding damage to the pelvic plexus. Next, the paravesical and obturator spaces are opened between the lateral

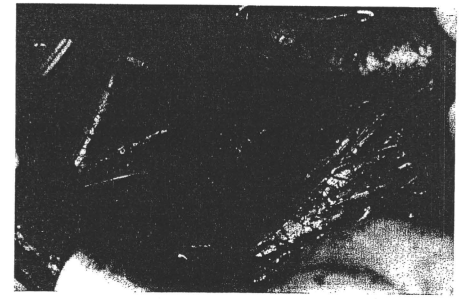

Fig. 2. Photo after a lateral lymph node dissection (LLND) with autonomic nerve preservation.

border of the internal iliac vessels and the external iliac artery. The lymphatic tissue next to the urinary bladder is cleared, sparing the vesical vessels and the distal branches of the plexus running to the anterior organs. Above the obturator channel, the obturator nerves and vessels are identified and cleared of all lymphatic tissue. After completion of the LLND, the following structures can be well identified in each lateral compartment (Fig. 2): the internal and external iliac vessels, the obturator nerve, the vesical arteries, and the pelvic nerve plexus.

According to Japanese guidelines, when involved lateral lymph nodes are suspected on preoperative evaluation or intraoperative findings, extended lateral dissection is recommended *(110,117)*. This encompasses en bloc excision of the internal iliac vessels and resection of the autonomic nervous system.

Nerve-Sparing Surgery and LLND

Various types of nerve-sparing surgery exist, even differing by institution. Total automatic nerve preservation encompasses preservation of the superior hypogastric plexus, the bilateral pelvic nerves and the inferior hypogastric plexuses (Figs. 3 and 4). Other forms include uni- and bilateral pelvic nerve and plexus preservation, with dissection of the superior hypogastric plexus. When lateral lymph nodes are suspected to be involved, no autonomic nerve preservation is conducted.

It is established that damage to the autonomic nervous system is associated with urinary and sexual function disturbance. Moreover, the psychological effects of surgery itself, having a serious disease and sometimes a stoma, have effects of functional well-being. Although there are good questionnaires, functional results are liable to subjectivity and variations in terminology. Table 2 shows functional results of Japanese studies in which total autonomic nerve preservation combined with LLND are reported. Also, results of partial preservation techniques and autonomic nerve preservation without LLND are mentioned. Generally, urinary dysfunction can be prevented by nerve preservation, except in the report by Matsuoka et al. In this study, however, many patients with partial preservation were included in the

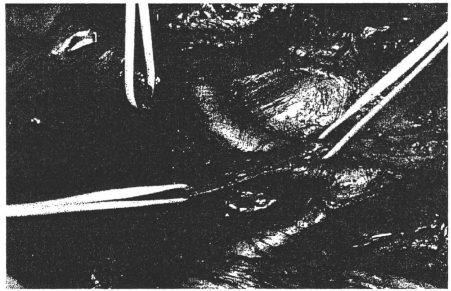

Fig. 3. Photo after nerve preservation of the superior hypogastric plexus.

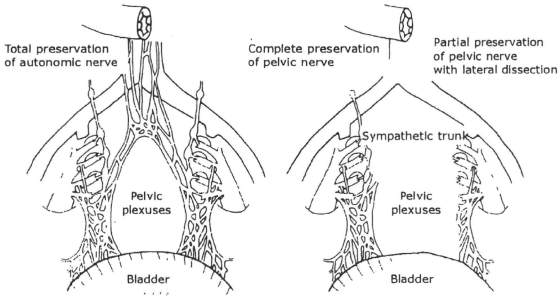

Fig. 4. Scheme of types of LLND with autonomic nerve preservation.

calculations. Sexual dysfunction varies greatly, with erectile dysfunction ranging from 10 to 83%. Ejaculatory dysfunction remains a major problem, ranging from 18 to 90%, even after nerve preservation. Unfortunately, the number of published results is too limited to make any definitive conclusions regarding outcomes comparing LLND to standard TME.

Table 2
Functional results of LLND with ANP, LLND with partial ANP and TME with ANP

			LLND with total ANP				*LLND with partial ANP*		
Name author	Year	No	UD	ErD	EjD	No	UD	ErD	EjD
Hojo *103*	1991	10	NS	28%	40%	18	NS	77%	100%
Moriya *104*	1995	31	2%	10%	32%	30	29%	73%	93%
Masui *129*	1996	98	NS	10%	18%	17	NS	47%	53%
Mori *107*	1998	45	0%	>45%	45%	64	6%	>45%	75%
Ameda *130*	2005	27	0%	83%	75%	25	8%	92%	92%
			LLND with total ANP				*TME with total ANP*		
Maeda *131*	2003	65	15%	27%	38%	12	25%	20%	40%
Matsuoka *132*	2005	15	47%	NS	NS	42	24%	NS	NS
Kyo *118*	2006	15	27%	50%	90%	22	18%	10%	30%

UD urinary dysfunction, *ErD* erectile dysfunction, *EjD* ejaculatory dysfunction, *NS* not stated

The explanation of urinary and sexual dysfunction following nerve-sparing surgery is ascribed to traction and injury to the nerves during mobilization and electrocautery required for LLND *(118)*. Although care is taken during mobilization and manipulation of the rectum in order to reach the lateral compartments, the risk of injury remains.

Patterns of Local Recurrence

In the many decades of LLND surgery in Japan, constant evaluation has been undertaken with the intent of preventing over-treatment and minimizing morbidity *(119)*. Nowadays the policy in many Japanese hospitals is case-oriented, adapting the degree of surgical resection and autonomic nerve preservation to the extent of cancer spread *(120)*. Whereas the standard procedure was to perform bilateral LLND in case of advanced rectal cancer during the 1970s and 1980s at the NCCH in Tokyo, unilateral LLND has been performed more recently.

In a recent study, we evaluated the treatment at the NCCH for rectal carcinoma at or below the peritoneal reflection between 1993 and 2002, evaluating patterns of local recurrence and risk factors for local recurrence *(53)*. Preoperative evaluation consisted of CT-imaging and endoscopic ultrasonography for all patients. Based on preoperative imaging and intraoperative findings, standard TME was performed in T1 or T2 disease without suspected lymph nodes. LLND was added to TME in stage T3 or T4 rectal cancer at or below the peritoneal reflection, or when positive mesorectal lymph nodes were suspected. Unilateral LLND was performed when the tumor was located laterally in the low rectum and bilateral LLND when the tumor was located centrally. When the lateral lymph nodes were 1 cm or larger on preoperative imaging or intraoperative findings, bilateral extended lymph node dissection was performed, consisting of dissection of the complete internal iliac arteries and the autonomic nerve system. When there was no suspicion on positive lateral lymph nodes, autonomic nerve preservation was carried out.

Of the 351 patients studied, 145 had standard TME surgery without LLND, 73 unilateral LLND and 133 patients bilateral LLND. LLND was performed in significantly younger patients and more often in combination with a nonsphincter-saving procedure, compared to patients who had not undergone LLND. The tumors in the LLND patients had higher T- and N-stages and were significantly larger. Comparing the clinicopathological characteristics

Table 3
Sites of local recurrence

	All patients			*Only N+ patients*		
Site of local recurrence	*Unilateral LLND (n = 73)*	*Bilateral LLND (n = 133)*	*P*	*Unilateral LLND (n = 32)*	*Bilateral LLND (n = 74)*	*P*
Lateral	5 (5.6)	4 (3.3)		4 (13.2)	3 (4.6)	
Ipsilateral	3 (4.5)			3 (9.9)		
Contralateral	2 (2.2)			1 (3.3)		
Presacral	2 (2.8)	0 (0)		2 (6.7)	0 (0)	
Perineal	2 (2.8)	2 (1.7)		1 (3.1)	2 (3.4)	
Anterior	0 (0)	1 (0.9)		0 (0)	1 (1.8)	
Anastomotic	3 (4.2)	2 (1.6)		3 (9.8)	2 (3.0)	
Unknown	0 (0)	1 (0.8)		0 (0)	1 (1.4)	
Total	**12**	**10**		**10**	**9**	
5-Year LR-rate	**15.4%**	**8.3%**	**0.06**	**32.8%**	**14.2%**	**0.04**

Values in parenthesis are the 5-year local recurrence rates per subsite

between the unilateral and the bilateral LLND, no significant differences were found, except that unilateral LLND was combined with autonomic nerve preservation more often.

The mean lymph node harvest was 21 lymph nodes following standard TME. After unilateral LLND, the mean number of recovered lymph nodes was 38 and following bilateral LLND, this was 45 ($p = 0.004$). Overall lymph node involvement was 42% and lateral lymph node involvement was 10%. Jump metastases (negative mesorectal lymph nodes and positive lateral lymph nodes) occurred in 3% (7/207) of the patients with a LLND.

The results of this study showed a 5-year local recurrence rate of 6.6% in rectal cancer at or below the peritoneal reflection by Japanese surgery. This primarily surgical approach compares favorably to the results in Western countries, where neoadjuvant therapy is adopted as the standard treatment in order to reduce local recurrence rates. Therefore, the Japanese concept of removing the lateral basins of lymph node spread can be considered successful. Patterns of local recurrence are shown in Table 3.

This study, although retrospective, provides further evidence of disease outside the TME envelope in higher stage tumors. Bilateral LLND (5-year local recurrence rate of 14%) resulted in improved local control versus unilateral LLND (5-year local recurrence rate of 33%) in *N+* patients (Table 3). Persistent disease in lateral lymph nodes that is left behind may account for some local recurrences, as would occur in standard TME surgery. However, if that was the case, it would be expected that most recurrences would originate in this lateral basin. In this study, we noted that not all local recurrences involved the lateral side walls. In fact, most recurrences could not be explained by the anatomical position of the lateral lymph nodes. One can only speculate about other mechanisms, including how tumor cells seed into the surgical resection bed. It is possible that removal of the lateral lymph nodes also removes (microscopic) tumor cells which are in transit in the lateral lymph flow route, which could otherwise leak back into the surgical wound. This would explain why results of unilateral dissection is inferior to bilateral dissection, resulting in more local recurrence in not only the lateral subsite, but in the presacral, perineal, and anastomotic subsites as well.

The rationale behind unilateral LLND is that the contra-lateral autonomic nervous system remains intact, as urinary and sexual dysfunction following nerve-sparing surgery is often ascribed to traction and injury to the nerves during mobilization and electrocautery required for LLND *(118)*. Unfortunately, we have no data on urinary and sexual function of this cohort and are unable to report on the results after unilateral LLND with nerve preservation. Therefore, the question whether functional results are truly better remains unanswered.

The tumors of the patients who underwent TME without LLND were smaller and less advanced compared to LLND patients. This lower staging is reflected in better survival. The fact that only one patient who had standard TME surgery had local relapse (5-year local recurrence rate of 0.8%) is striking. The selection of low-risk disease by pre- and intraoperative evaluation therefore appears accurate. Interestingly, however, pathologic evaluation showed that about 30% of patients undergoing TME had T3 or N-positive disease. Pathology appears to reveal more metastatic lymph nodes than preoperative imaging, but these (micro) metastases do not appear to impact local control. "Jump" metastases occurred in only 3% of LLND patients, thus, when mesorectal lymph nodes are unsuspected, the risk of lateral lymph node recurrence is very low.

Current Practice in Japan

Since 2003, the NCCH in Tokyo has coordinated a national multicenter randomized clinical trial comparing TME with or without LLND, with autonomic nerve preservation. The preoperative evaluation consists of endoscopic ultrasonography and MRI-imaging. Patients with histologically confirmed adenocarcinoma below the peritoneal reflection and clinical stage II or III disease are included. Patients with lymph nodes larger than 10 mm or with tumor invasion into other organs are not in included in the trial. Final accrual of 600 patients was estimated to be completed in 2009.

For patients with T1 or T2 disease without suspected lymph node involvement, TME without (neo)adjuvant therapy is the standard treatment in Japan. For T4-disease and disease with overt lateral metastases, there is currently a debate whether neoadjuvant (chemo)radiation needs to be added to TME plus LLND.

Lymphoscintigraphy

Sentinel node mapping is still in an experimental phase in colorectal cancer *(121,122)*. With this approach, visibility is compromised, especially in the rectum which is mainly located retroperitoneally. Ex vivo procedures make injection of blue dye and identification of the blue nodes possible. However, in order to identify extramesorectal lymph node drainage patterns, lymphoscintigraphy might be the most promising method. Although lymphoscintigraphic localization of sentinel nodes seems reliable in early colorectal cancers, the method might not be as accurate for the indication of lateral lymph node spread in advanced disease. Studies have shown inferior results in large rectal tumors, tumors with extensive metastases, tumors invading adjacent organs and patients receiving preoperative chemoradiation therapy *(123)*. Nonetheless, recent studies have revealed interesting results.

Funahashi et al *(124)*. injected 99 m Tc-colloid around the tumor preoperatively using a fiberscope or rectoscope. Following tumor resection by TME, "hot" nodes were identified in the pelvis using a radioactive tracer and the area of the highest nodal emission defined as the draining lymph node basin of the tumor. Following this, LLND was performed and all lymph nodes were examined histologically and immunologically. From the distribution of the hot

nodes, a lateral type and a mesorectal type of lymph node basin could be identified. Seventeen of the 39 tumors (44%) drained mainly laterally and of these 17, 8 had involved lymph nodes (4 positive lateral nodes). In the 22 patients with mesorectal draining lymph node basins, one false-negative was found, which demonstrated a lateral lymph node metastasis. The authors concluded that the concordance between lymph node metastases and the draining lymph node basin was good.

Another study was performed by Kawahara et al *(125)* in order to identify the first lateral draining lymph node. Indocyanine green was injected into the rectum in 14 patients with T3 lower rectal cancer. A LLND was performed with usage of infrared ray electronic endoscopy to identify the lymph nodes. Drainage of indocyanine green into the lateral lymph nodes was seen in 6 of 14 patients (43%), which were all detected intraoperatively with the infrared endoscopy. Lymph node drainage was limited exclusively to the peri-internal iliac artery nodes.

Thus, although further studies are needed to assess its accuracy, lymphoscintigraphy may play a future role in detecting the presence of lateral lymph basins in individual patients in the East. In the absence of lateral involvement, patients might be spared from LLND. In the West, this method should also be considered in the management of lateral nodes.

Locally Advanced Disease: (Chemo)Radiation or LLND?

To date, there are no randomized studies comparing preoperative (chemo)radiotherapy and TME with LLND in similar patients, making it difficult to make a statement about which regimen is preferred in advanced rectal carcinoma. In a few nonrandomized studies, an attempt has been made to compare (neo)adjuvant treatment with LLND.

Watanabe et al *(126)* divided 115 patients into four subgroups; Rad+LLND–, Rad+LLND+, Rad–LLND+, and Rad–LLND–. Local recurrence rates, disease-free survival and overall survival were not significantly different between Rad+LLND– and Rad–LLND+. The authors suggested that preoperative radiotherapy could be an alternative for LLND in patients with low rectal carcinoma.

Kim et al *(127)* compared 176 patients with TME and postoperative chemoradiotherapy or TME combined with a LLND. The 5-year overall survival and disease-free survival rates did not differ significantly. In patients in the LLND-group with stage III low rectal cancer, local recurrence rate was 16.7%, which is higher than 7.5% in the postoperative CRT group ($p=0.044$). However, the LLND group may have contained "very low" rectal cancers *(128)*.

In our recent study, we analyzed the differences between Japan and the Netherlands in the treatment of low rectal cancer, with focus on the patterns of local recurrence *(58)*. The Dutch group consisted of patients of the TME trial; 376 patients underwent TME for low rectal cancer and 379 received preoperative radiotherapy (RT+TME). Three hundred twenty-four patients were analyzed in the Japanese group, who received extended surgery consisting of LLND and a wider abdominoperineal excision. The majority received no (neo)adjuvant therapy. The Dutch and Japanese patients were matched as closely as possible by selecting only tumors up to 7 cm from the anal verge, which was considered the level of the peritoneal reflection. Five-year local recurrence rates were 6.9% for the Japanese NCCH group, 5.8% in the Dutch RT+TME group and 12.1% in the Dutch TME group. It could be concluded that Japanese extended surgery and RT+TME result in good local control, as compared to TME alone.

Because of the differences in patient groups mentioned previously, it remains difficult to compare Japanese and Western series. A trial currently being conducted in Japan will show whether a LLND can truly prevent local recurrence, and is designed to study the effect of a "preventive" LLND, as patients with definite lateral metastases are not included. Modern MRI

may allow identification of patients with clearly involved or suspected lateral lymph nodes. In these cases, LLND is probably not enough and it is uncertain whether the nodal metastases can be fully sterilized by preoperative chemoradiation. Additionally, the risk for disseminated disease is high and prognosis unfavorable for lateral lymph node-positive patients. For these patients, it may be wise to consider a combination of treatments: neoadjuvant chemoradiation therapy, LLND and possibly adjuvant systemic therapy.

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