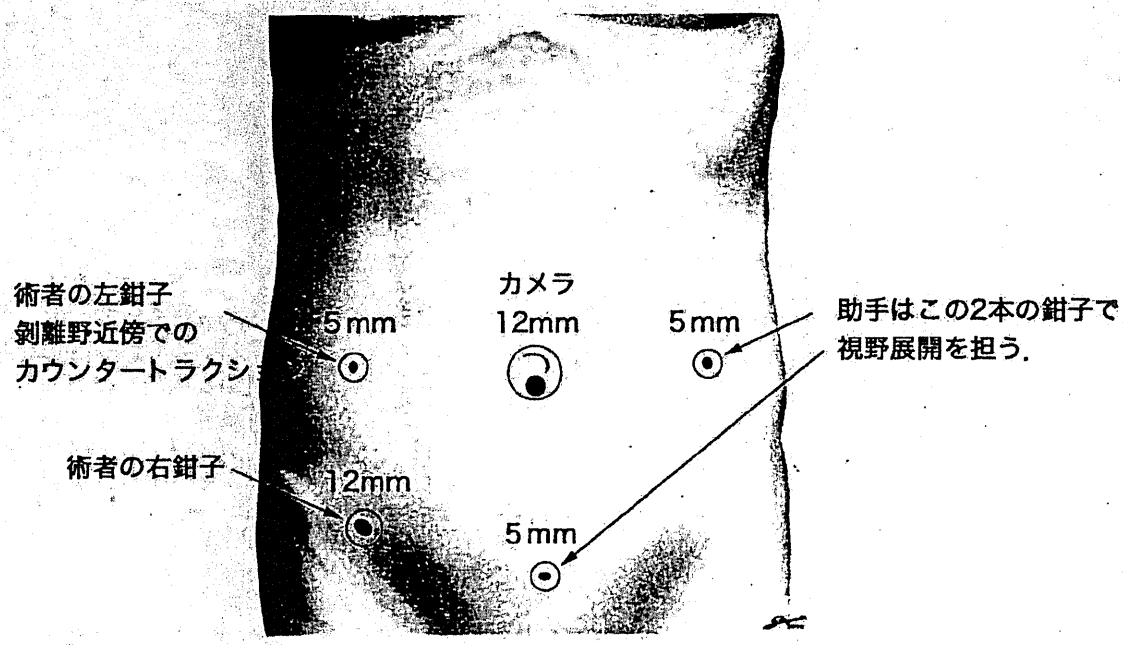

図7　ポート挿入と鉗子の役割

臍部，右上，右下，左上および恥骨上部の計5ポートにて手術する．臍ポートよりカメラを挿入し，右側の2つのポートは術者が使用する．左上のポートは助手鉗子に使われる．恥骨上ポートは，主に剝離が小骨盤腔に及ぶときに直腸を把持するために使われる．

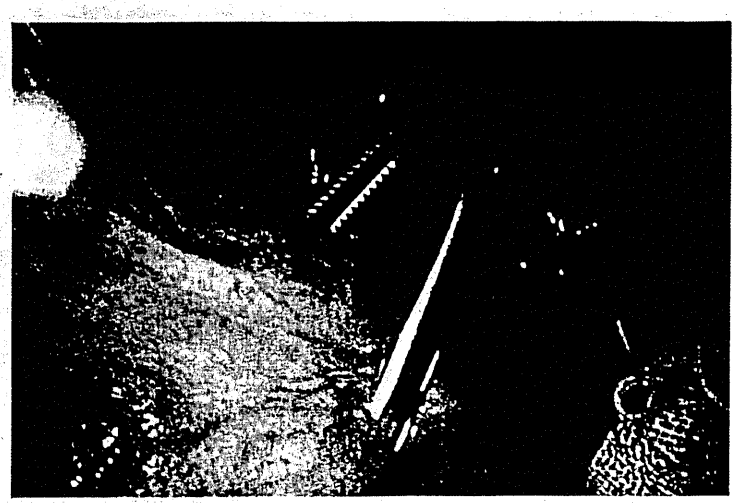

図8　恥骨上ポートからの直腸把持と視野展開

恥骨上ポートより腸クランプ用鉗子を挿入し，直腸壁が損傷しないように大きく把持する．TMEが施行される間，この鉗子は常に直腸を把持したままとし，前後左右にその鉗子を動かし，左上からの助手鉗子で膀胱後面(あるいは子宮後面)を把持し腹側に展開する．この定型化された展開法により，術者の2本の鉗子は視野展開でなく剝離に専念できる．

9 ESR/Miles 手術

上方郭清は通常の直腸癌切除術のごとく行うので今回は詳細を省略する．口側の人工肛門予定腸管部は腹腔内で切離しておく．

小骨盤腔でのTME手技に際しては，それぞれの局面でメルクマールとなる解剖学的構造物を認識しながらの剝離を行う．

まず直腸後壁では，岬角よりやや尾側あたりで直腸後腔に入り，光沢のある直腸固有筋膜をまず認識する．後壁剝離は直腸固有筋膜に沿って進むべきである．助手鉗子で直腸を腹側に牽引し，術者左鉗子で下腹神経前筋膜を把持し，背側にトラクションをかけることによりシャープな剝離層が認識できる(図9)．

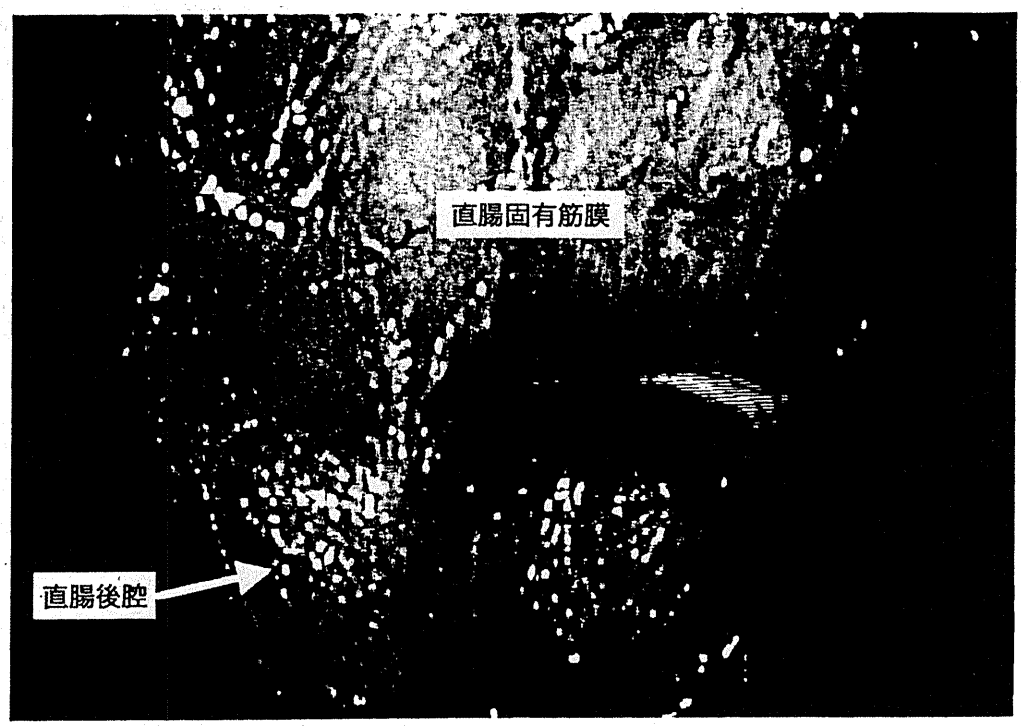

図9　直腸後腔で直腸固有筋膜を露出

光沢のある直腸固有筋膜を岬角よりやや尾側あたりでまず認識する．このあたりでは直腸後腔は比較的幅の広い空間として認識される．後壁剝離では直腸固有筋膜につかず離れず進む．助手鉗子で直腸を腹側に牽引し，術者左鉗子で下腹神経前筋膜を背側にトラクションをかけることにより膜と膜の間の剝離層が認識できる．

直腸前壁剝離では，Denonvilliers 筋膜がメルクマールとなる．従来 TME ではこの筋膜を直腸壁側につけた剝離が標準的に行われてきたが，腹腔鏡下 ISR の適応となるような T2までの病変であれば，Denonvilliers 筋膜を精嚢側につけて剝離することで，膜の解剖に則った自律神経の良好な温存が可能となる(図10)．この場合理論的には Denonvilliers 筋膜と直腸固有筋膜の間で剝離し，精嚢が直接露出しないこととなるが，しばしば直腸固有筋膜を認識しにくい症例(特に女性)が存在するのも事実である．Miles 手術の適応となる症例においては，Denonvilliers 筋膜を温存しうるか否かに関するコンセンサスには至っていない．私見では前壁に主座をおく病変でなければ，Denonvilliers 筋膜を温存しても十分な CRM が確保され，根治切除となる症例もあると思われる．

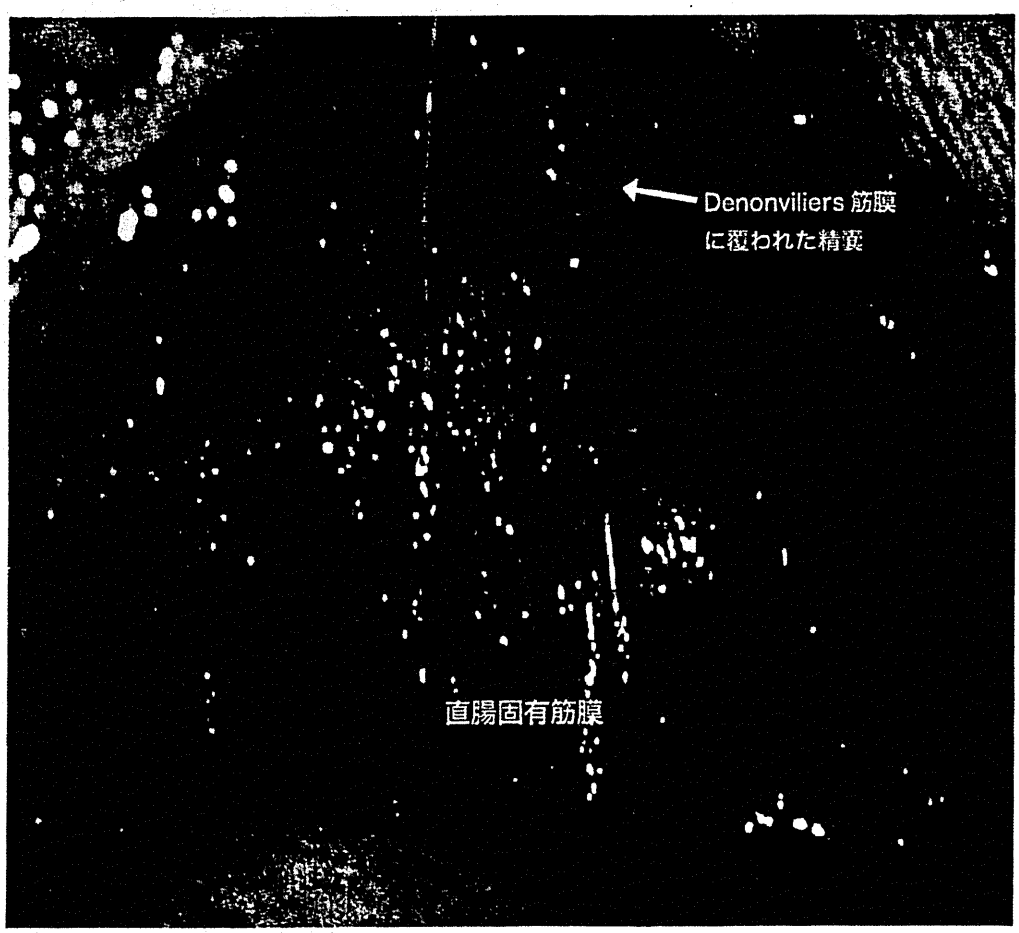

図10　直腸前方での剝離層の選択

直腸前壁剝離では，白色のやや厚い膜と認識される"Denonvilliers 筋膜"が重要な指標となる．腹腔鏡下 ISR の適応となるような T2までの病変であれば，Denonvilliers 筋膜と直腸固有筋膜の間を剝離することで，神経血管束を含む自律神経が解剖学的に温存されることとなる．

直腸側壁の剝離は，後壁と前壁の剝離が十分行われた後に行うことで骨盤神経叢付近の視野展開が明瞭になる．まずは右側壁での剝離を行うが，このとき恥骨上ポートからの直腸把持鉗子を左側に展開し，助手鉗子で膀胱(あるいは子宮)を腹側に展開することでテント状に張った骨盤神経叢が良好に視認できる．神経の損傷を防ぐにはテント状に見える神経の頂点で切離すべきであり，そのためにはこのようなトラクションの効いた視野作りが非常に重要である(図11)．いわゆる側方靭帯を切離した後は，出血する構造物はなく，直腸右側で挙筋上腔に達する(図12)．

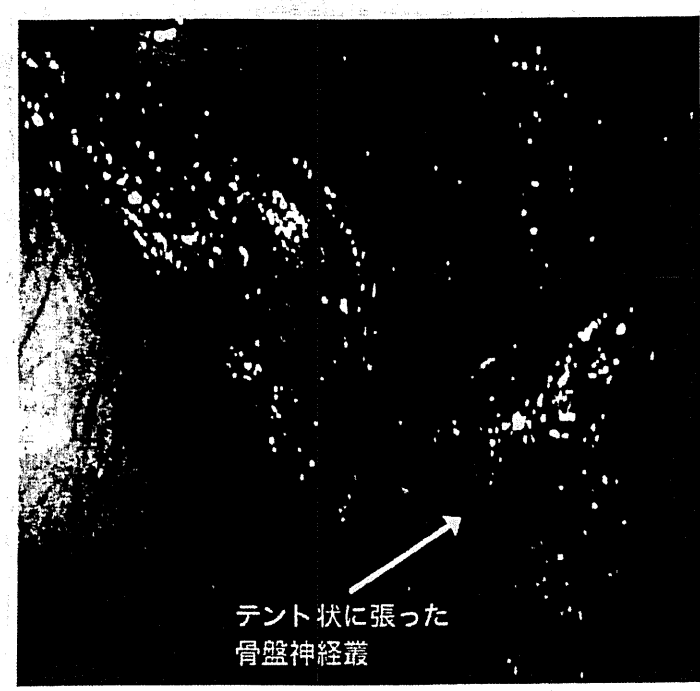

図11　直腸側方での神経温存
恥骨上ポートからの直腸把持鉗子を左側，頭側方向に牽引し，助手鉗子で膀胱(あるいは子宮)を腹側に展開することでテント状に張った骨盤神経叢が良好に視認できる．

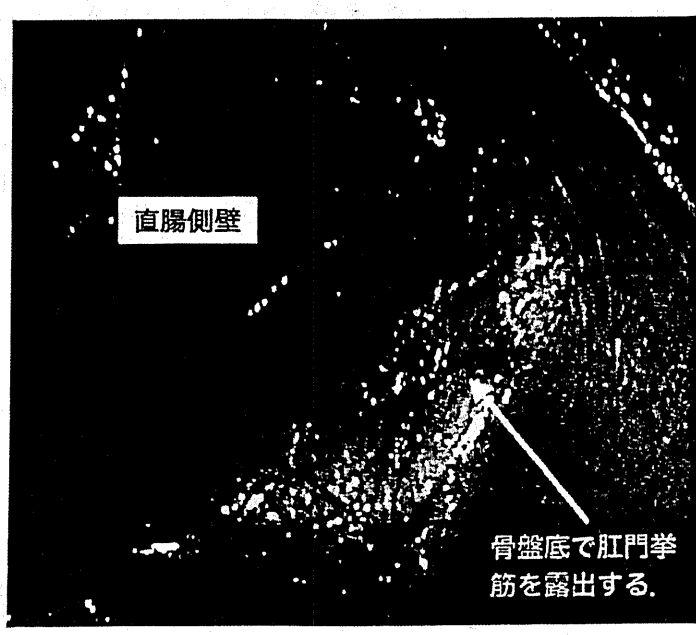

図12　肛門挙筋の露出(ISR 症例)
いわゆる側方靭帯を切離した後は，ある程度鈍的な剝離で出血することなく肛門挙筋が露出される．Miles 手術では，「恥骨直腸筋が直腸に巻き付くライン」を同定するまで剝離を完全に行うことはせず，やや離れた位置で肛門挙筋を切り込む．従ってこの写真は，Miles 手術においては肛門挙筋を露出しすぎていることになる．

2)腹腔鏡下肛門挙筋切離

Miles手術とISRの手術操作で違いがでてくる点は，直腸側方において恥骨直腸筋や恥骨尾骨筋の露出の程度である(図13)．本来Miles手術の適応とされる症例はISRの切除線では根治性に疑問のある症例である．したがって十分なCRMを確保するためにMiles手術では恥骨直腸筋の露出はできるだけ避けなければならない．ある程度肛門挙筋の繊維が見え始めたら，腫瘍に近づきすぎないよう剝離を終える．肛門挙筋の切離は腹腔側から行っても会陰側から行っても良いが，筆者らは腹腔鏡下手術では腹腔側から肛門挙筋を切離することが多い．まず左右の側壁において直腸壁から十分な距離をおいて肛門挙筋(恥骨尾骨筋あたり)を切離する．この切離には超音波凝固切開装置が有用である．肛門挙筋を切離すると坐骨直腸窩の脂肪に到達するので，左右側壁において広く坐骨直腸窩と連続させる．後壁においてはISRのようにHiatal ligamentの直腸壁よりで切離する必要はなく，むしろligamentの尾骨ぎりぎりで切離するイメージで，できる限り腹腔側から切離する．後壁で剝離はあまり無理する必要はない．肛門操作で尾骨をメルクマールに剝離すると後壁は容易に腹腔内と連続されるからである．

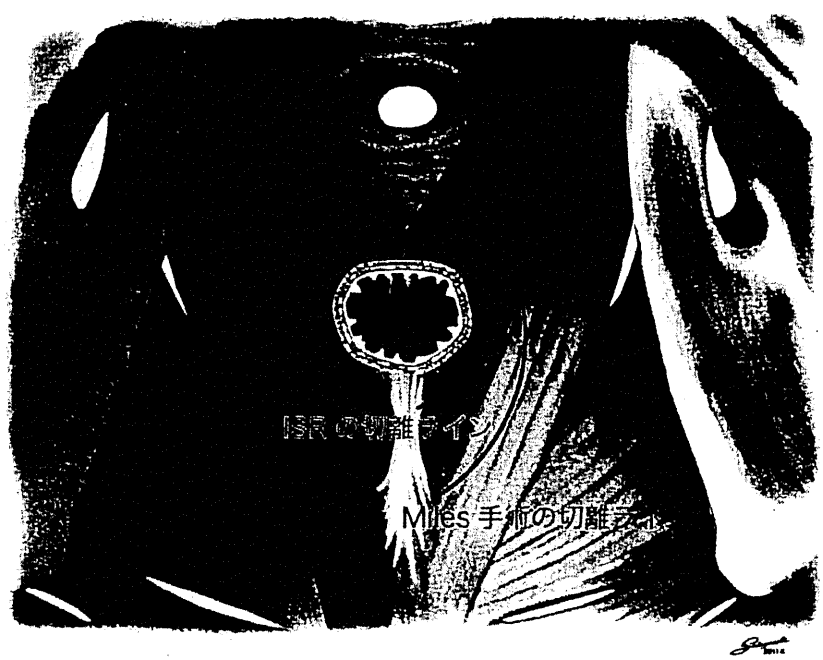

図13　Miles手術とISRにおける肛門挙筋の切離線の違い

Miles手術では，十分なRadial marginを確保するために恥骨直腸筋の露出はできるだけ避けなければならない．ある程度肛門挙筋の繊維が見え始めたら，腫瘍に近づきすぎないよう剝離を終える．一方ISRではMiles手術と異なり，恥骨直腸筋が直腸に巻き付くラインを完全に露出することが重要である．

3)肛門操作

砕石位で足を上方に挙上する．肛門の腹側，背側，左右に清潔な覆布を新しくかける．

Miles 手術ではまず肛門周囲に針糸を全周にかけて肛門を閉鎖し，汚物の術中排出を防ぐ．肛門周囲の皮膚切除ラインは，後方では尾骨，側方では坐骨結節，前方は球海綿体筋のそれぞれ内側とし電気メスで切り込み始める(図14)．

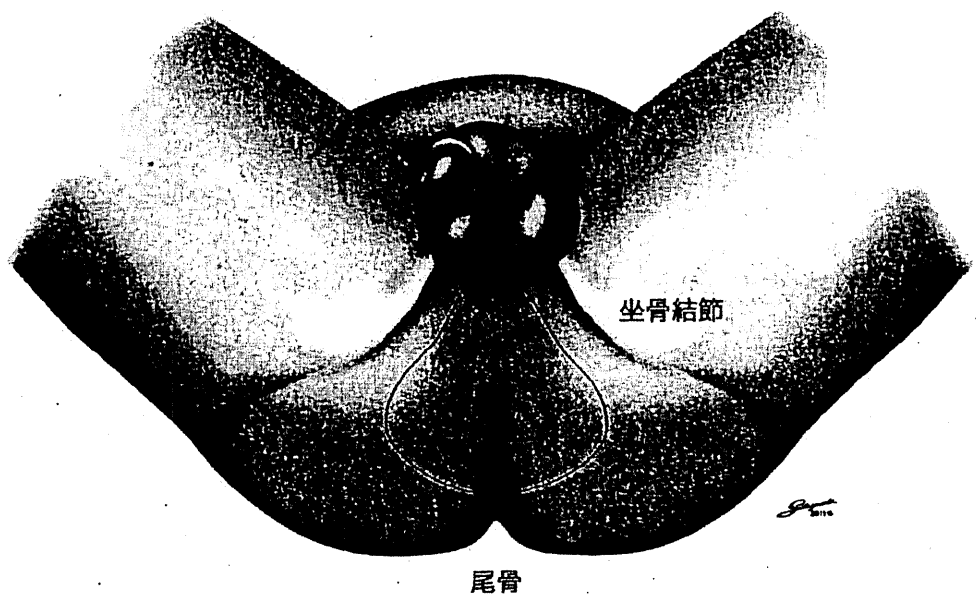

図14　Miles 手術における会陰皮膚切開

肛門周囲の皮膚切除ラインは，後方では尾骨，側方では坐骨結節，前方は球海綿体筋のそれぞれ内側とし電気メスで切り込み始める．

続いて坐骨直腸窩の脂肪を十分切除するように切離する．肛門挙筋に到達する前に2時と10時方向に下直腸動脈の枝が確認されるため，この血管を処理する．腹腔内から肛門挙筋を切っていれば，側方では容易に腹腔内と連結する．後方は尾骨の下端を目指して剝離を進めるが，この場所でも腹腔側と交通させることが比較的容易に可能である．一度どこかで腹腔側とつながれば，触診を手がかりに左右側壁から後壁にかけて広く腹腔内と連続した空間を作ることができる．左右側壁および後壁で2/3周くらい剝離されるまで肛門挙筋を切離すると前壁剝離が残るが，この部位の剝離層の認識が難しい．ここでは前立腺や膣後壁と直腸壁との境界の認識に難渋することがあるため，十分な牽引のもとでの剝離操作が望ましい．腹腔側で切離した口側腸管を肛門より引き出し，手前に牽引し切離を進める(図15)．

このトラクションにより前壁の剝離は行いやすくなることが多い．標本が提出されたら，骨盤底を十分生理食塩液で洗浄し，会陰創を閉鎖する．会陰部より閉鎖式ドレーンを入れる術者もいるが筆者は腹部からのドレーンのみで対応している．会陰操作が終わったら，腹部に戻り止血確認後術前にマーキングした左下のストーマサイトにS状結腸を誘導し，単孔式ストーマを造設する．腹膜外経路か腹腔経路かは議論のあるところであるが，腹腔鏡下Miles手術の場合には，腹腔経路でstomaを造設することが最近は多い．

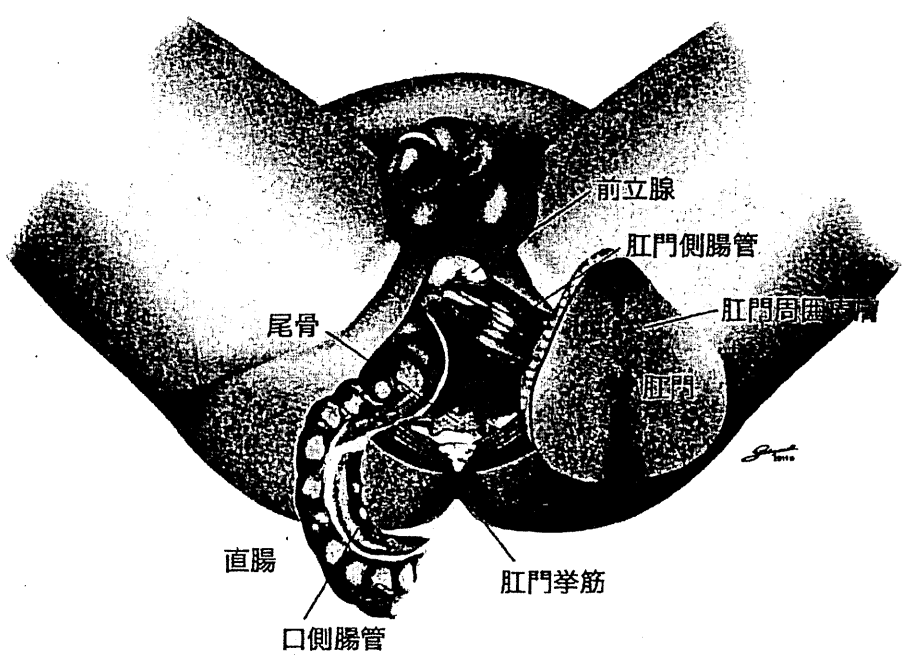

図15　Miles手術における直腸前壁の剝離方法

左右側壁および後壁で2/3周くらい剝離されるまで肛門挙筋を切離したあとは腹腔側で切離した口側腸管を肛門より引き出し，手前に牽引し切離を進める．

この操作により前立腺や膣と直腸との境界がわかりやすい．

2. 腹腔鏡補助下 ESR の手術手技

先ほども述べたが ESR の手技は難しく，完全腹腔鏡下での手技が成熟していないのが現状であろう．T3以深例では，ときに触診の力を借りて，腫瘍側で外括約筋を切除し，腫瘍のない側は ISR と同じ剝離層を選択することが多い．したがって，ESR は通常開腹で行われるべき手術であり，骨盤操作を腹腔鏡補助下で行う ESR の手術手技について以下に述べる．

ESR では腫瘍の局在を術中にいかに認識しながら剝離を進めていくかが非常に重要な要素である．腫瘍がない部位においては ISR と同様の考え方で恥骨直腸筋が直腸に巻き付くラインを完全に露出する（図16）．一方でT3以深の腫瘍がある部分では若干の安全域を広く取りながら肛門挙筋の一部(多くは恥骨直腸筋)を合併切除するラインを想定して腹腔内から外括約筋群を切除する(図16)．もちろんこの領域では Miles 手術と同様に坐骨直腸窩の脂肪が露出される．筆者らの施設では ESR は外科的マージンの十分な確保が主たる目的であるため，広範囲な外括約筋の系統的切除は通常行っていない．

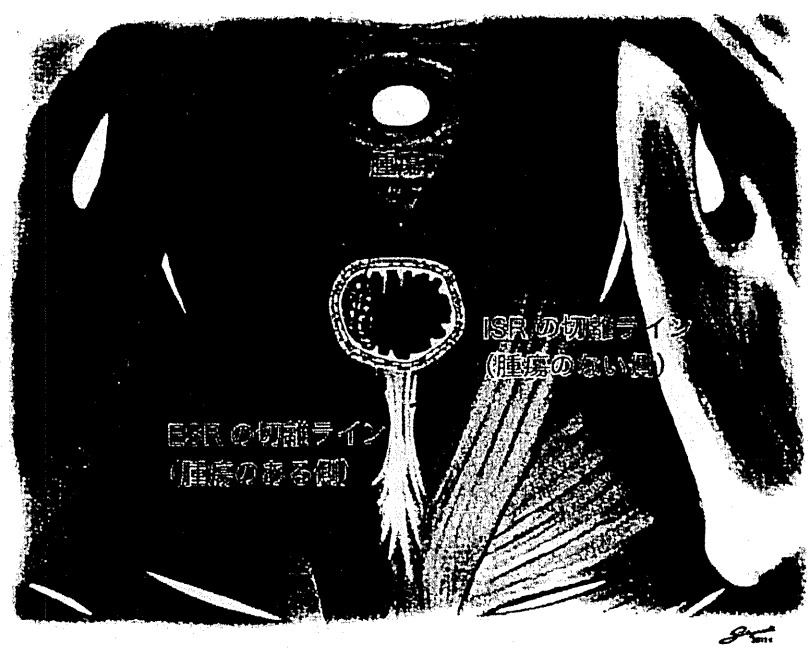

図16　ISR と ESR における切離線の違い

ESR では腫瘍のない側は ISR と同じように「恥骨直腸筋」が直腸に巻きつくラインを意識し，そこから内外括約筋間の離を行う．腫瘍がある側では，CRM を確保するために腫瘍直下で肛門挙筋を合併切除するよう外回りの切離線をおく．

1)腫瘍のない側での剝離：通常のISRの剝離層

まずは腫瘍のない側での剝離を先に行うことが多い．それは通常のISRのように定型的な剝離が可能であり，ESRを付加しなくても十分な外科的マージンを確保できることが多いためである．

まずは直腸の左右側方に腫瘍がない場合には，できるかぎり側壁側で恥骨直腸筋が直腸に巻き付くラインをしっかり同定する．なぜならこの部分での括約筋間剝離が最も容易であるからである．恥骨直腸筋をセッシなどで外側に展開し，肛門管における内外括約筋間の剝離を開始する．連合縦走筋繊維の同定が困難な症例があるため，肛門挙筋や外肛門括約筋の筋繊維を露出しながら剝離を進めることで正しい層取りと認識しうる．また肛門管内ではときに血管の流入があるので，十分な止血をこまめに行う．ここでの出血は正しい剝離層の認識にきわめてマイナス材料となる．このように腹腔側から左右側壁で肛門管の剝離を腫瘍から2cm肛門側まで剝離する．左右側方での剝離を終えると，後方正中にカーテン状につり上がった「hiatal ligament」が認識される．側方ですでに剝離された恥骨直腸筋の走行に注意しながら後方でのhiatal ligamentの切離線を決める．ここでの切離線の選択も腫瘍がない場合には通常のように尾骨寄りで切りすぎないように注意する(図17)．一方後壁に腫瘍がある場合には，hiatal ligamentの尾骨よりで切離する．側方での剝離と異なり後方の剝離は，粗な結合組織間の剝離というよりは，錯綜した筋繊維を切離するような感じと表現できる．後方も側方と同じように腫瘍を2cm越えるあたりまで十分剝離する．

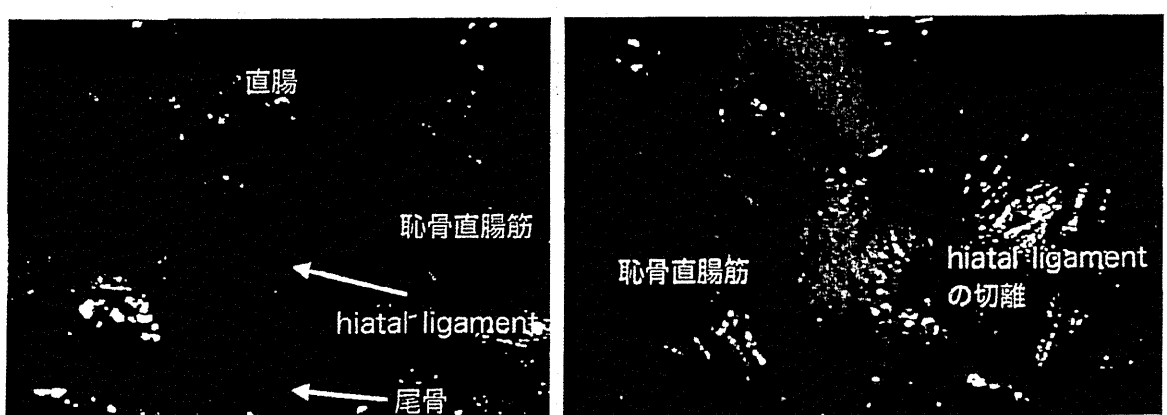

図17　hiatal ligamentの同定とその切離

肛門管後壁では，側壁のような疎な結合組織の間のシャープな剝離層として認識されず，むしろ筋繊維を含んだ固い構造物を切離するイメージで剝離される．したがって直腸側壁剝離を先行させた方がhiatal ligamentの切離レベルを認識しやすい．

9 ESR/Miles 手術

2)腫瘍側での剝離：ESR の剝離層

ESR の適応となる T3以深症例において，腫瘍のある側では腫瘍先進部で十分な外科的マージンを確保する必要がある．この場合，肛門管近傍に主座のある腫瘍では，肛門挙筋や外括約筋の合併切除が余儀なくされる．腫瘍側で ESR を行う場合の切離線の選択は Miles 手術の肛門挙筋の切り方(図16)と同様のものである．すなわち直腸壁に近づきすぎずにある程度外側から肛門挙筋を切除する必要がある．Miles 手術と同様に肛門挙筋を切除すると坐骨直腸窩の脂肪が露出することなる．ESR を行う領域は腫瘍学的安全性を考慮し，やや広めに行っておいたほうがよい．

3)肛門操作

ローンスター開肛器をかけ肛門を十分展開する．筆者らは腫瘍と一緒に直腸内洗浄を２ℓ生理食塩液で行っている．腫瘍下縁と肛門縁(Anal verge：AV)，歯状線(Dentate line：DL)，ヘルマン氏線(Hermann's line：HL)との距離を計測し，粘膜切離ラインを決める．腫瘍部は１～２cm の肛門側マージンを確保するが，腫瘍のない側では，やや口側の切離ラインをおくこともある．

ここでデザインされた切離ラインにより，図４で示したような内肛門括約筋の温存度が異なることになる．

直腸粘膜を切離すると，腸管軸と同方向の繊維方向を示す連合縦走筋が見える．ISR ではこの縦繊維を切除側につけるようにすると外肛門括約筋の輪状繊維が視認できる．肛門操作で最も信頼性のあるメルクマールはこの「輪状繊維」に沿って剝離することである(図18)．全周で１cm くらい剝離した後に腸管を閉鎖し，遊離癌細胞の術中散布をできるかぎり回避する．さらに剝離を進めていくと多くは後壁か側壁で腹腔側の剝離ラインと連続される．この時腹腔側から鉗子を剝離された内外括約筋間に誘導するとよいメルクマールとなる．腹腔内から外括約筋を切除した部位は腫瘍の深達度が最も深い領域，すなわち外科的マージンの確保において重要な領域であるため，それ以外の領域で腹腔内と連続させ，腫瘍学的に最も難しい部分は最後に残しておくことがコツであると思う．

一度腹腔内と連続されれば，前壁を残して後壁と側壁はすべて腹腔内と連続するように剝離を進めることは比較的容易である．前壁が腫瘍の主座である場合の治療選択はとくに難しい．特に男性で前立腺に近接する腫瘍では，前立腺合併切除や骨盤内臓全摘(TPE)の適応となるケースも含まれるが，そこまで必要のない症例でも前立腺ぎりぎりでやや出血を覚悟しながら剝離を進めることで根治切除が得られることも経験される．開腹手術では口側腸管を前もって切離しているので，切離腸管を肛門から取り出して(反転)十分なトラクションをかけながら剝離を行う．

全周で腹腔内と連続したら肛門より標本を引き出す．肛門管を生理食塩液で十分洗浄した後に，肛門管の状況を確認するとおそらく思ったよりも広い範囲で坐骨直腸窩の脂肪が露出していることが多い．筆者らは残った外括約筋や肛門挙筋で脂肪を被覆して肛門管形成を行うことが多い．ただし，外括約筋の切除程度により坐骨直腸窩脂肪の完全な被覆が難しい症例も経験される(図19)．

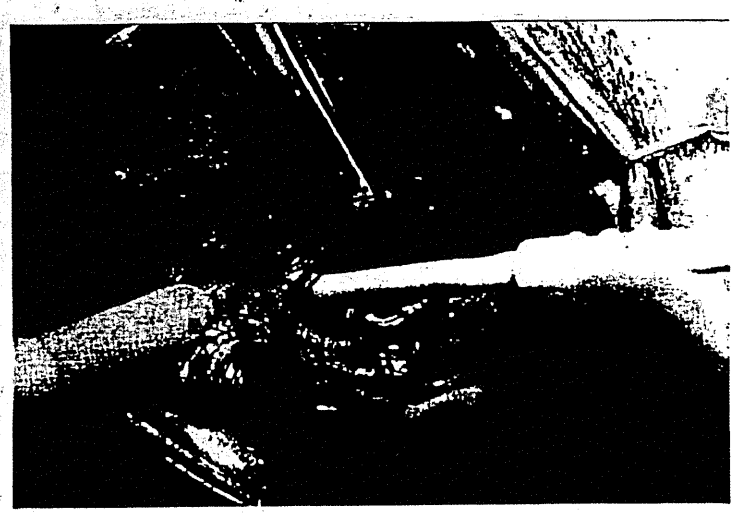

図18　肛門側からの括約筋間剝離

肛門操作では外肛門括約筋の「輪状線維」がメルクマールとなる．この輪状線維に沿って剝離を進め腹腔側と連続させる．

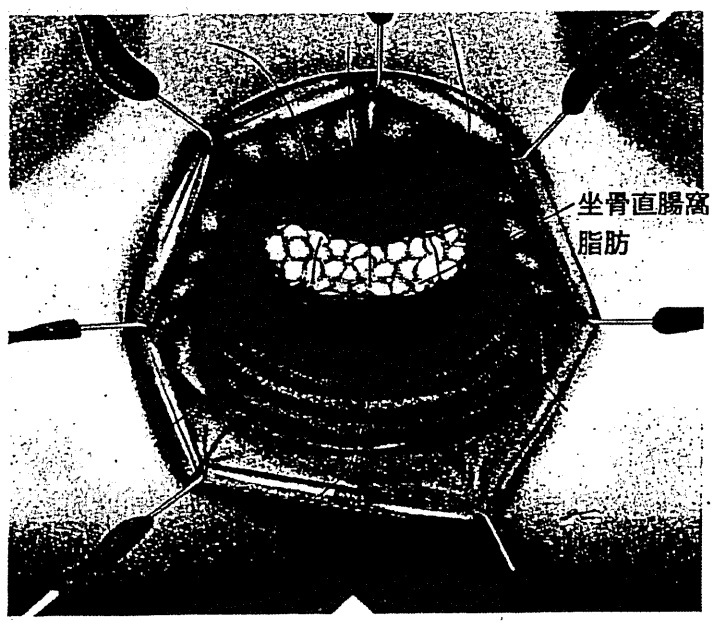

図19　外括約筋群の欠損部の形成

ESRで外括約筋群が切除された部分は坐骨直腸窩の脂肪が露出している．温存された肛門挙筋と外肛門括約筋を縦方向にrepairし外括約筋群を形成し欠損部を被覆する．

図20 Coloanal anastomosis(CAA)
結腸肛門吻合は，45度間隔で8針はマットレス縫合を行い，それぞれの針間で2針追加することにより計24針にて手縫い吻合する．

結腸肛門吻合は，45度間隔で８針はマットレス縫合を行い，それぞれの針間で２針追加することにより計24針にて手縫い吻合する(図20)．

通常 Ileostomy を造設後，腹側から骨盤底に19Fr J-VACドレーンを留置し手術を終える．

おわりに

ESR と Miles 手術の二つの術式は，まさに肛門温存できるか否かの境界に相対する手術である．ESR により外括約筋を合併切除することにより根治的切除に至る症例は少なからず存在し，その結果永久人工肛門を回避することは技術的には可能となってきた．しかし術後肛門機能が許容しうる範囲を超えるほど悪い場合には，Miles 手術による永久人工肛門のほうが QOL が保たれるケースがあるのも事実である．両者の適応を判断するための腫瘍学的成績と機能的成績の蓄積が今後待たれる．

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Clinical Significance of the Mesorectal Extension of Rectal Cancer: A Japanese Multi-institutional Study

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Objective: The aim of this study was to emphasize the importance of a subclassification in the TNM staging system of rectal cancer.

Background: The clinical significance of the mesorectal extension of rectal cancer is unclear.

Patients and Methods: Data from 463 consecutive patients with stage IIa disease (T3N0) undergoing curative surgery at 28 institutes were analyzed. The measurement of the distance of the mesorectal extension (DME) was histologically evaluated. Risk factors for recurrence, for the optimal cutoff point of the DME, independent prognostic factors, and for survivals were studied using receiver operating characteristic curve and logistic and Cox regression analyses. Survivals were calculated using the Kaplan-Meier method.

Results: A value of 4 mm was determined as the optimal cutoff point. The patients were subdivided into 2 groups: DME $\leq$ 4 mm and DME > 4 mm at the optimal cutoff point. DME > 4 mm had the greatest impact on recurrence-free survival [$P = 0.00023$, hazard ratio (HR): 2.26, 95% confidence interval (95% CI): 1.465-3.492, L/U ratio: 0.420] and was an independent adverse prognostic factor ($P = 0.00323$, HR: 1.97, 95% CI: 1.254-3.091). The distant metastasis rate in DME > 4 mm was higher 16.7% than that in DME $\leq$ 4 mm ($P = 0.00177$, OR: 2.61, 95% CI: 1.430-4.761). The incidence of local recurrence was not influenced by DME. The recurrence-free 5-year survival rate in DME $\leq$ 4 mm was significantly better than that in DME > 4 mm (86.6% vs 71.3%, $P = 0.00015$, HR: 0.44, 95% CI: 0.286-0.683). The cancer-specific survival rate in DME $\leq$ 4 mm was also significantly better than that in DME > 4 mm (91.3% vs 82.2%, $P = 0.000664$, HR: 0.52, 95% CI: 0.325-0.843).

Conclusions: A subclassification according to mesorectal extension based on a 4-mm cutoff point is needed for the TNM staging system. However, further prospective study is necessary to prove reproducibility and validity of the cutoff point.

(*Ann Surg* 2011;253:704–710)

The current TNM staging system is now the standard for colorectal cancer staging and well reflects prognosis. However, the mesorectal extension in rectal cancer also seems to influence recurrence or prognosis, but the mesorectal extension is not mentioned in the TNM staging system. Although the UICC proposed optional subdivisions for T3 and T4 tumors in 1993,[1] the clinical significance of the mesorectal extension in rectal cancer has still not been recognized. Several reports from a single institute have shown the prognostic heterogeneity of T3 rectal cancers.[2–10] However, these reports have used different prognostic cutoff points for subdividing the mesorectal extension in T3 tumor, that is, microscopic invasion,[5] more or less than 2 mm,[3] 3 mm,[6,10] 4 mm,[2,8,9] 5 mm,[4] or 6 mm.[7] Those reports are still controversial because of the small number of patients, only a small amount of data, and being from a single institute, and insufficient statistical analyses. A Swiss Registry Study on Colorectal Cancer (SAKK) showed that the 30-month survival rate was better in N0 patients with mesorectal extension $\leq$ 5 mm (cited from reference 11). Based on multi-institutional large investigation, Merkel et al[4] analyzed the data of the Erlangen Registry for Colo-Rectal Carcinomas (ERCRC) and the German prospective multicenter study of the Study Group Colo-Rectal Carcinoma (SGCRC), and they reported that the prognosis was significantly better in patients with mesorectal extension $\leq$ 5 mm. We have now analyzed the multi-institutional large amounts of data from the Study Group of the Japanese Society for Cancer of the Colon and Rectum (JSCCR), and we report these findings here. The present study emphasizes the clinical importance of defining appropriate substages within the TNM staging system.

PATIENTS AND METHODS

Approval from the Ethics Committee of both the JSCCR and the local institutional review board was obtained to allow review of the medical records and to permit follow-up patient contact. Data were reviewed on 1091 patients enrolled from 28 institutes that were members of the Study Group of the JSCCR on Extramural Mesorectal Extension of Rectal Cancer. All patients had a primary rectal adenocarcinoma that was located in the lower two-thirds of the rectum. Total mesorectal excision and histologically defined curative surgery were performed between 1995 and 1999. Neither preoperative radiotherapy nor neoadjuvant chemotherapy was performed in these enrolled patients. Of the 1091 patients, 1055 possessed available clinicopathological information and were eligible for analysis. Thirty-six patients were excluded because of insufficient clinical and follow-up information. Of the 1055 patients, the present study was focused on those 463 with stage IIa disease. The clinicopathological data and follow-up system were based on the Japanese rules defined by JSCCR.[12] They were restaged according to the pathological TNM classification (6th edition).[13] Most institutes established a postoperative follow-up examination period of 5 to 10 years. The follow-up system consisted of measurement of serum tumor marker, chest x-ray, and abdominal ultrasound examination every 3 months for the first 3 years and then every 6 months for the next 2 years. When the development of recurrence was suspected, the final diagnosis was made using CT and/or MRI and other diagnostic tools. Local recurrence

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Supplemental digital content is available for this article. Direct URL citation appears in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

No author has any conflict of interest.

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ISSN: 0003-4932/11/25304-0704
DOI: 10.1097/SLA.0b013e3182119331

was defined as the presence of radiologically confirmed or histologically proven tumor nonhematogenously occurring in the pelvis within the field of the initial surgery. Distant metastasis included hematogenous metastases to the liver, lung, bone, brain, kidney, and other organs. The other recurrences were defined as a recurrence except local recurrence and distant metastasis, that is, peritoneal dissemination, intra-abdominal, para-aortic, subclavicular, mediastinal, and inguinal lymph node metastases. The outcomes of all patients were investigated as carefully as possible. As of January 1995, the eligible surviving patients had been followed for a median of 86 months (range, 1–166). Of these patients, 89.2% were followed for at least 3 years, and 81.9% for at least 5 years.

Measurement of Mesorectal Extension

All surgically resected specimens were opened up along the antimesenteric side. The specimens were fixed in 20% formalin for at least 48 hours after being pinned to a wooden or corkboard. Then, 1 or more longitudinal sections of the tumor were sliced at the point of maximum extramural invasion. Those sections were embedded in paraffin after being divided into some blocks of suitable size, which were then routinely processed for hematoxylin-and-eosin and elastica-Van-Gieson staining. In those sections, the tumor category T3 was subdivided on the basis of the histological measurement of the maximum depth of invasion beyond the outer border of the muscular layer (in millimeters). Without any knowledge of clinical information, the histological measurement was assessed. Hematoxylin-and-eosin-stained sections are presented in Figure 1. When the outer border of the muscular layer was completely identifiable (sometimes identifiable as fragments of muscle), the distance from the outer border of the muscular layer to the deepest part of the invasion was measured (Fig. 1a). When the outer border of the muscular layer was not entirely identifiable because of destruction by the invasion or excessive inflammatory reaction, an estimate of the outer border was obtained by drawing a straight solid line between both break points in the muscular layer (Fig. 1b).

Statistical Methods

Statistical analysis was performed using computer software of StatView 5.0 and JMP 7.0 (SAS Institute, Inc, Cary, NC) for Windows. All clinicopathological independent variables (12 items) were encoded for analysis: sex (female: 0, male: 1), size of tumor ($\leq$ 5 cm: 0, $>$ 5 cm: 1), location of tumor (middle-third: 0, lower-third: 1), gross type (expansive: 0, infiltrative: 1), histology [well-differentiated adenocarcinoma: 0, others (moderately, poorly differentiated, and mucinous adenocarcinoma): 1], lymphatic invasion [negative-to-minimal invasion (ly0–1): 0, moderate-to-severe invasion (ly2–3): 1], venous invasion [negative-to-minimal invasion (v0–1): 0, moderate-to-severe invasion (v2–3): 1], operative methods [sphincter-saving operation (SSO): 0, abdominoperineal resection (APR): 1], lateral pelvic lymph node dissection (no: 0, yes: 1), autonomic-nerve-saving operation (yes: 0, no: 1), postoperative chemotherapy (no: 0, yes: 1), and mesorectal extension ($\leq X$ mm: 0, $> X$ mm: 1). Total recurrence (absent: 0, present: 1), distant metastasis (absent: 0, present: 1), local recurrence (absent: 0, present: 1), and survival (alive: 0, dead: 1) were coded as dependent variables. A receiver operating characteristic (ROC) curve was used to find an expected cutoff point. The continuous variable of distance of the mesorectal extension (DME) was applied to ROC analysis. Both univariate logistic regression analysis for recurrence and multivariate Cox regression analysis for recurrence-free survival were used to confirm the optimal cutoff point of mesorectal extension. The Cox regression analysis was also used to analyze the independent prognostic factors for recurrence-free survival. The Kaplan-Meier method and the logrank test were used for calculating survival rates. Some detailed P values were calculated using the chi-square calculator on the Web site of www.swogstat.org/statoolsout.html. The level for statistical significance was determined at $P < 0.05$ and the confidence interval (CI) was determined at the 95% level.

RESULTS

Histogram of Distance of Mesorectal Extension

The DME in the 463 rectal cancers was histologically measured. The mean DME was 4.2 ± 4.2 mm, and the median DME was 2.9 mm (range, 0.1–30) (Fig. 2).

Postoperative Recurrence Pattern

Postoperative total recurrence occurred in 89 (19.2%) of the 463 patients. Twenty-five patients (5.4%) had local recurrence only, and 49 patients (10.6%) had distant metastasis only. The remaining 15 patients had other recurrences, that is, peritoneal dissemination, intra-abdominal, para-aortic, subclavicular, mediastinal, and inguinal lymph node metastases (Table 1).

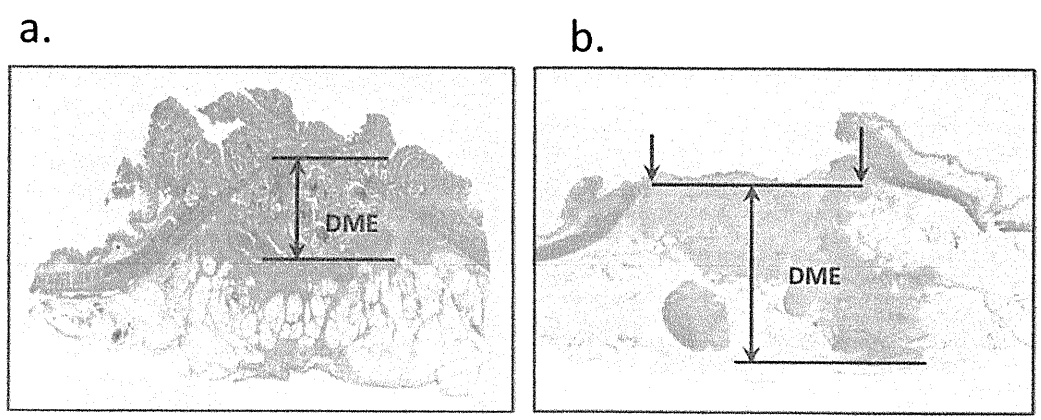

FIGURE 1. Measurement of DME. A, When the outer border of the muscular layer was completely identifiable, the distance from the outer border of the muscular layer to the deepest part of the invasion was measured (mm). B, When the outer border of the muscular layer was not entirely identifiable, an estimate of the outer border was obtained by drawing a straight solid line between the both break points of the muscular layer.

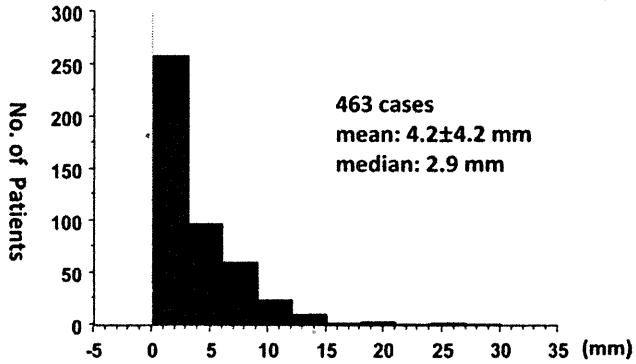

FIGURE 2. Histogram of DME. The mean DME is 4.2 ± 4.2 mm, and the median DME is 2.9 mm (range, 0.1–30).

TABLE 1. Postoperative Recurrence Pattern in Patients With Stage IIa (T3N0)

No. of Patients	Local only	Distant only	Local plus Distant	Others*	Total Recurrence
463	25 (5.4)	49 (10.6)	0	15	89 (19.2)

*Peritoneal dissemination, intra-abdominal, para-aortic, subclavicular, mediastinal, and inguinal lymph node metastases.

Risk Factors for Postoperative Recurrence

The risk factors for postoperative recurrence are listed in Table 2. The gross type (infiltrative type; odds ratio [OR]: 2.06, 95% CI: 1.100-3.840, $P = 0.0240$), histology (others: OR: 1.70, 95% CI: 1.010-2.852, $P = 0.0457$), lymphatic invasion (ly2–3; OR: 3.07, 95% CI: 1.777-5.303, $P = 0.000058$), venous invasion (v2–3; OR: 2.31, 95% CI: 1.426-3.726, $P = 0.000656$), and operative methods (APR; OR: 1.67, 95% CI: 1.050-2.660, $P = 0.0303$) were significant risk factors for postoperative recurrence.

Statistical Analysis of Cut-off Points

The mean value of 4.2 mm was considered as a cutoff point from the DME histogram (Fig. 2). The ROC curve showed 4.2 mm as the cutoff value expecting postoperative recurrence at a high true positive rate (sensitivity: 0.5169), low false positive rate (1 − specificity: 0.3262), high accuracy rate (0.6436), high positive likelihood ratio (1.5846), high positive predictive value (0.2738), high OR (2.2097), and low chi-square P value (0.0012) among other cutoff points (Fig. 3). The ROC curve analysis was reasonable as a statistical model [AUC (area under curve): 0.617, OR: 1.05, 95% CI: 0.9991-1.1050, $P = 0.0541$]. A value of 4 mm was then considered as an appropriate cutoff point. Univariate logistic regression analysis showed that the value of 4 mm was a good cutoff point that had significant influence on postoperative recurrence ($\chi^2 = 10.997$, OR: 2.21, 95% CI: 1.383-3.531, $P = 0.00091$). The L/U ratio (lower/upper limits of CI) showed high reliability (0.392), among other cutoff points (Table 3a). Multivariate Cox regression analysis confirmed that the value of 4 mm was an optimal cutoff point that had the greatest impact on recurrence-free 5-year survival, among all other cutoff points (highest $\chi^2 = 13.567$, higher hazard ratio [HR]: 2.26, 95% CI: 1.465-3.492, highest LU ratio: 0.420, and lowest $P = 0.00023$) (Table 3b). Therefore, the patients were subdivided into 2 groups: DME ≤ 4 mm and DME > 4 mm.

Independent Prognostic Factor for Recurrence-free Survival

The significant variables extracted in Table 2 and the cutoff point of 4 mm determined in Table 3 were analyzed to determine the independent prognostic factors for recurrence-free survival using Cox regression analysis. The variables are listed in Table 4. Lymphatic invasion (ly2–3; $\chi^2 = 9.873$, HR: 2.22, 95% CI: 1.351-3.659, L/U ratio: 0.369, $P = 0.00168$), venous invasion (v2–3; $\chi^2 = 5.446$, HR: 1.73, 95% CI: 1.091-2.727, L/U ratio: 0.400, $P = 0.01961$), and DME (> 4 mm; $\chi^2 = 8.674$, HR: 1.97, 95% CI: 1.254-3.091, L/U ratio: 0.406, $P = 0.00323$) were extremely higher independent adverse prognostic factors for recurrence-free survival. Especially, DME > 4 mm was the most reliable adverse predictor with the highest value of L/U ratio.

Distant Metastasis and Local Recurrence

The distant metastasis rate was significantly higher in DME > 4 mm (16.7%, $\chi^2 = 9.774$, OR: 2.61, 95% CI: 1.430-4.761, $P = 0.00177$). The local recurrence showed no significant difference at the cutoff point ($\chi^2 = 2.733$, $P = 0.09829$) (Table 5).

Recurrence-free and Cancer-specific Survivals

The 5- and 10-year recurrence-free survival rates of DME ≤ 4 mm in patients were 86.6% and 85.3%, respectively. They were significantly better than those of DME > 4 mm (HR: 0.44, 95% CI: 0.286-0.683, $P = 0.00015$) (Table 6, Fig. 4a). The 5- and 10-year cancer-specific survival rates of DME ≤ 4 mm were 91.3% and 82.2%, respectively. They were significantly better than those of DME > 4 mm (HR: 0.52, 95% CI: 0.325-0.843, $P = 0.00664$) (Table 6, Fig. 4b).

DISCUSSION

The TNM staging system of the International Union Against Cancer[13] and American Joint committee on Cancer[14] are now the standards for colorectal cancer staging. The current sixth edition of the *AJCC Cancer Staging Manual* includes refinements in colorectal cancer staging that are based on large data sets from the National Cancer Data Bases.[15] The stage is the strongest predictor of survival, and the TNM staging system definitively reflects prognosis. Although subclassification of T3 was not essential, measurement of the depth of extramural soft tissue invasion has been previously proposed by some authors.[11,16] Several reports from a single institute showed the prognostic heterogeneity of T3 rectal cancers.[2–10] However, those authors reported a variety of prognostic cutoff points for subdividing mesorectal extension of T3/T4 tumors. Willett et al[3] constructed 3 subgroups of the depth of invasion: < 2 mm, 2 to 8 mm, and ≥ 8 mm. The recurrence-free survival in patients with T3N0 was significantly different: 87% vs 57% vs 36%, respectively. They recommended selecting patients with rectal cancer for postoperative adjuvant therapy by the depth of invasion into the perirectal fat. Harewood et al[17] assessed the mesorectal extension from a different approach, using preoperative endoscopic ultrasound. They reported that all T3 rectal tumors were not equal, and recurrence-free survival was significantly better in patients with minimally invasive T3 disease (≤ 2 mm). Tokoro et al[10] selected the cutoff point of 3 mm although the number of investigated patients was very small (26 patients). They reported that T3N0 patients with a mesorectal extension ≥ 3 mm had worse recurrence-free 5-year survival, and that ≥3 mm was an adverse independent prognostic factor for recurrence-free survival. However, Picon et al[6] showed no prognostic significance of mesorectal extension at a cutoff point of 3 mm. At the cutoff point of 4 mm, mesorectal extension more than 4 mm was confirmed as an independent adverse prognostic factor for survival by some multivariate

TABLE 2. Risk Factors for Postoperative Recurrence in Patients With Stage IIa (T3N0) Using Univariate Logistic Regression Analysis

Variable	No. of Patients	Rate of Recurrence	χ^2	OR (95% CI)	*P*
Sex					
Male vs female	331 vs 132	19% vs 19%	0.010	1.03 (0.614-1.715)	0.9222
Size of tumor					
> 5 cm vs ≤ 5 cm	231 vs 225	19% vs 20%	0.019	0.97 (0.608-1.541)	0.8907
Location of tumor					
Lower third vs middle third	300 vs 163	21% vs 15%	2.425	1.50 (0.901-2.487)	0.1194
Gross type					
Infiltrative vs expansive	56 vs 400	30% vs 18%	5.097	2.06 (1.100-3.840)	0.0240
Histology					
Others vs well	301 vs 162	22% vs 14%	3.994	1.70 (1.010-2.852)	0.0457
Lymphatic invasion					
ly2–3 vs ly0–1	74 vs 387	36% vs 16%	16.178	3.07 (1.777-5.303)	0.000058
Venous invasion					
v2–3 vs v0–1	135 vs 327	29% vs 15%	11.609	2.31 (1.426-3.726)	0.000656
Operative methods					
APR vs SSO	197 vs 266	24% vs 16%	4.690	1.67 (1.050-2.660)	0.0303
Lateral pelvic LN dissection					
Yes vs no	261 vs 202	18% vs 21%	0.981	0.79 (0.498-1.258)	0.3219
Autonomic nerve saving					
No vs yes	14 vs 421	21% vs 19%	0.042	1.15 (0.312-4.199)	0.8384
Postoperative chemotherapy					
Yes vs no	168 vs 286	17% vs 20%	0.621	0.82 (0.501-1.343)	0.4307

well: well differentiated adenocarcinoma, others: moderately, poorly differentiated, and mucinous adenocarcinomaly 0–1, v0–1: negative to minimal invasion, ly2–3, v2–3: moderate to severe invasion, LN: lymph node APR: abdominoperineal resection, SSO: sphincter saving operation, OR: odds ratio, CI: confidence interval

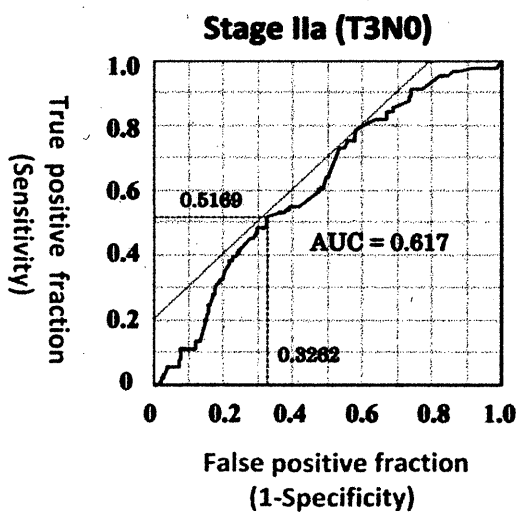

FIGURE 3. Cutoff point of DME using ROC curve analysis. The ROC curve analysis showed high sensitivity (0.5169), specificity (0.6737), positive likelihood ratio (1.5846), positive predictive value (0.2738), accuracy (0.6436), OR (2.2097), and smaller chi-square *P* (0.0012) at the cutoff point of 4.2 mm.

analyses.[2,8,9] Miyoshi et al[7] analyzed 2 different patient databases and decided the cutoff point at 6 mm. They reported that patients with mesorectal extension ≥ 6 mm had worse 5-year survival in stage II disease. Merkel et al[4] prospectively analyzed the different patient data from the multicenter institutes (ERCRC and SGCRC). They used 5 mm for the cutoff point of mesorectal extension of T3 tumor and subdivided T3 tumors into T3a (≤ 5 mm) and T3b (> 5 mm). They reported that in the ERCRC series the T3b patients with N0 had worse cancer-related 5-year survival. An extended T3 classification (T3a, T3b) was proposed. Thus, many authors have emphasized the prognostic heterogeneity of the mesorectal extension. Although it seems to be very difficult how to theoretically set an optimal cutoff value, it must be essential to subdivide the TNM staging system. Statistical analysis based on a large data set from multicenter institutes is required to clarify whether mesorectal extension is independent as a risk factor and how to reflect this in the TNM staging system. Based on our statistical analyses, DME > 4 mm was strongly associated with postoperative recurrence and recurrence-free survival, compared with DME ≤ 4 mm. It may be said that DME is one of the risk factors for postoperative recurrence. So, the optimal cutoff point was theoretically set to a value of 4 mm. Then, the mesorectal extension was divided into 2 groups: DME ≤ 4 mm and DME > 4 mm.

As a popular independent prognostic factor, lymphovascular invasion has been often reported. The DME was also reported as an independent prognostic factor for disease-free survival or cancer-specific survival.[2,3,7,9,10] In our multivariate analysis, lymphatic and venous invasion were also extracted each as a powerful indicator with high reliability and DME.

The local recurrence at stage II after total mesorectal excision for rectal cancer has varied from 4% to 21%.[18–22] A multicenter prospective randomized trial organized by the Dutch Colorectal Cancer Group[23] reported that the 2-year local recurrence rate after

TABLE 5. Distant and Local Recurrence in Patients With Stage IIa (T3N0) at the Cutoff Point of 4 mm

Recurrence Pattern	DME	No. of Recurrence (%)	χ^2	OR (95% CI: L-U)	L/U ratio	*P*
Distant	≤ 4 mm (n = 295)	21 (7.1)		1		
	> 4 mm (n = 168)	28 (16.7)	9.774	2.61 (1.430-4.761)	0.300	0.00177
Local	≤ 4 mm (n = 295)	12 (4.1)		1		
	> 4 mm (n = 168)	13 (7.7)	2.733	1.98 (0.881-4.441)	0.198	0.09829

CI indicates confidence interval; DME, distance of mesorectal extension; L, lower limit; OR, odds ratio; U, upper limit.

TABLE 6. Cumulative Recurrence-free and Cancer-specific Survivals in Patients with Stage IIa (T3N0) at the Cutoff Point of 4 mm

a. Recurrence-free survival

TNM Stage	DME	at 5-years (%)	at 10-years (%)	HR (95% CI) for Recurrence	Logrank *P*
IIa (T3N0)	≤ 4 mm (n = 295)	86.6%	85.3%	0.44 (0.286-0.683)	
	> 4 mm (n = 168)	71.3%	71.3%	2.26 (1.465-3.492)	0.00015
	Total	81.1%	80.2%		

b. Cancer-specific survival

TNM Stage	DME	at 5-years (%)	at 10-years (%)	HR (95% CI) for Recurrence	Logrank *P*
IIa (T3N0)	≤ 4 mm (n = 295)	91.3%	83.2%	0.52 (0.325-0.843)	
	> 4 mm (n = 168)	82.2%	73.9%	1.91 (1.187-3.073)	0.00664
	Total	88.4%	79.2%		

CI indicates confidence interval; DME, distance of mesorectal extension; HR, hazard ratio.

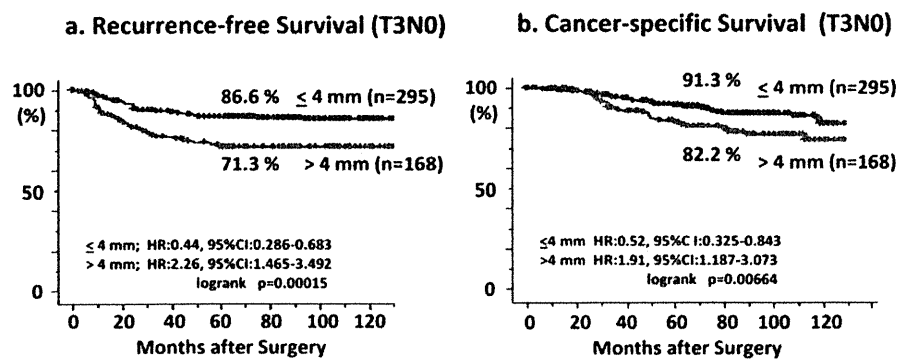

FIGURE 4. (A) Recurrence-free survival. The 5-year recurrence-free survival rate of DME ≤ 4 mm was 86.6%, which is significantly better than that of DME > 4 mm ($P = 0.00015$). (B) Cancer-specific survival. The 5-year cancer-specific survival rate of DME ≤ 4 mm was 91.3%, which is significantly better than that of DME > 4 mm ($P = 0.00664$).

associated with local recurrence.[24] In the present series, measurement of the CRM was not available because of too many missing values. A positive CRM (0 mm; tumor involvement directly at CRM) defined as noncurative resection by JSCCR was excluded from this analysis. Our data showed no significant difference concerning local recurrence at the cutoff point (Table 5). One reason for this difference may be the small number of patients developing local recurrence. Although the numbers may be too small to draw any definitive conclusions, the numbers did not seem to have an impact on local recurrence.

There have been only a few reports concerning distant metastasis and DME. Willett et al[3] reported statistically significant increase in distant-free survival (90%) in T3N0 patients with DME < 2 mm. Tokoro et al[10] also reported that distant metastasis differed significantly (< 3 mm; 0% vs ≥ 3 mm; 46.7%, $P = 0.01$), although the numbers of patients were very small. Based on our data, the DME was strongly associated with distant metastasis more so than local recurrence. As the DME becomes deeper, it is considered that many undetectable lymphovascular invasions exist in the mesorectal adipose tissues.

Many authors also have reported that the DME was an important predictor associated with recurrence-free and cancer-specific survivals. Merkel et al[4] reported that cancer-related 5-year survival of T3a tumors was significantly better than that of T3b (91.2% vs 77.2% at stage II). Similar outcomes in Dukes B (66% vs. 37%) at the cutoff value of 4 mm and in stage II (73% vs 52%) at the cut-off value of 6 mm have been reported.[2,7] Our statistical analysis also demonstrated that the DME was a powerful predictor for recurrence-free and cancer-specific survivals (Table 6). So, the DME has an extremely great impact on clinical significance in patients at stage IIa (T3N0). The subclassification in the TNM staging system consisting of a combination of T3 and DME is strongly proposed. Our statistical retrospective analysis was relevant to Merkel et al's[4] prospective

TABLE 3. Statistical Analysis of Cutoff Points for Postoperative Recurrence and for Recurrence-free 5-year Survival

a. Univariate Logistic Regression Analysis

DME (mm)	No. of Patients	Rate of Recurrence	χ^2	Logistic OR (95% CI: L-U)	L/U ratio	P
>1 vs ≤ 1	369 vs 94	22% vs 9%	8.030	3.02 (1.406-6.499)	0.216	0.00460
>2 vs ≤ 2	288 vs 175	24% vs 11%	12.062	2.64 (1.525-4.557)	0.335	0.00052
>3 vs ≤ 3	205 vs 258	24% vs 16%	5.523	1.71 (1.075-2.727)	0.394	0.02361
>4 vs ≤ 4	168 vs 295	27% vs 15%	10.997	2.21 (1.383-3.531)	0.392	0.00091
>5 vs ≤ 5	130 vs 333	29% vs 16%	9.673	2.15 (1.327-3.483)	0.381	0.00187
>6 vs ≤ 6	107 vs 356	29% vs 16%	8.293	2.10 (1.267-3.468)	0.365	0.00398
>7 vs ≤ 7	83 vs 380	27% vs 18%	3.403	1.69 (0.968-2.933)	—	0.06508
>8 vs ≤ 8	62 vs 401	19% vs 19%	0.001	1.01 (0.513-1.988)	—	0.9773
>9 vs ≤ 9	46 vs 417	22% vs 19%	0.208	1.19 (0.566-2.497)	—	0.6484
>10 vs ≤ 10	36 vs 427	19% vs 19%	0.001	1.02 (0.430-2.400)	—	0.9719

b. Multivariate Cox Regression Analysis

DME (mm)	No. of Patients	Recurrence-free 5-year Survival	χ^2	Logistic OR (95% CI: L-U)	L/U ratio	P
>1 vs ≤ 1	369 vs 94	78.1% vs 92.9%	7.519	2.96 (1.362-6.415)	0.212	0.00611
>2 vs ≤ 2	288 vs 175	75.3% vs 90.6%	11.702	2.54 (1.489-4.333)	0.344	0.00062
>3 vs ≤ 3	205 vs 258	75.8% vs 85.2%	5.450	1.68 (1.087-2.594)	0.419	0.01957
>4 vs ≤ 4	168 vs 295	71.3% vs 86.6%	13.567	2.26 (1.465-3.492)	0.420	0.00023
>5 vs ≤ 5	130 vs 333	69.9% vs 85.3%	12.842	2.23 (1.437-3.451)	0.416	0.00034
>6 vs ≤ 6	107 vs 356	69.3% vs 84.5%	11.390	2.18 (1.387-3.433)	0.404	0.00074
>7 vs ≤ 7	83 vs 380	72.9% vs 82.8%	3.909	1.66 (1.004-2.753)	0.365	0.04813
>8 vs ≤ 8	62 vs 401	78.5% vs 81.5%	0.347	1.20 (0.652-2.218)	—	0.55582
>9 vs ≤ 9	46 vs 417	76.3% vs 81.6%	0.882	1.37 (0.708-2.660)	—	0.34767
>10 vs ≤ 10	36 vs 427	78.3% vs 81.4%	0.211	1.20 (0.553-2.602)	—	0.64599

CI indicates confidence interval; DME, distance of mesorectal extension; HR, hazard ratio; L, lower limit; U, upper limit.

TABLE 4. Independent Prognostic Factor for Recurrence-free Survival in Patients With Stage IIa (T3N0) Using Multivariate Cox Regression Analysis

Variable	Recurrence-free 5-year Survival	χ^2	HR (95% CI: L-U)	L/U ratio	P
Gross type					
inf vs. exp	69.8% vs. 82.7%	1.861	1.49 (0.840-2.639)	—	0.17251
Histology					
others vs. well	78.5% vs. 85.9%	3.098	1.59 (0.949-2.658)	—	0.07839
Lymphatic invasion					
ly2–3 vs. ly0–1	61.8% vs. 85.0%	9.873	2.22 (1.351-3.659)	0.369	0.00168
Venous invasion					
v2–3 vs. v0–1	71.7% vs. 85.5%	5.446	1.73 (1.091-2.727)	0.400	0.01961
Operative methods					
APR vs. SSO	77.1% vs. 84.0%	2.352	1.42 (0.907-2.222)	—	0.12512
DME					
> 4 mm vs. ≤ 4 mm	71.3% vs. 86.6%	8.674	1.97 (1.254-3.091)	0.406	0.00323

APR indicates abdominoperineal resection; CI, confidence interval; DME, distance of mesorectal extension; exp, expansive; HR, hazard ratio; inf, infiltrative; L, lower limit, LN, lymph node; SSO, sphincter saving operation; U, upper limit.

surgery alone with total mesorectal excision in stage II patients was 5.7%. Those data were comparable with the results of our study on local recurrence after total mesorectal excision (Table 1). However, there have been only a few reports on the relevance between DME and local recurrence or distant metastasis. Willett et al[3] reported a statistically significant increase in local-free survival (93%) in T3N0 patients with DME < 2 mm. Merkel et al[4] reported that the local recurrence rate was significantly higher in T3b tumor more than 5 mm (N0; 15.4%), compared with T3a tumor up to 5 mm (N0; 5.5%) in the ERCRC data, but was not significant in the SGCRC data. Miyoshi et al[7] did not recognize the relevance concerning local recurrence between DME > 6 mm and ≤ 6 mm. Many authors also did not recognize the relevance between DME and local recurrence. The circumferential resection margin (CRM) of rectal cancer is strongly

results and strongly supports their proposal of T3 classification. The reproducibility and applicability of this proposed staging system to other situations should be evaluated in further prospective studies.

CONCLUSIONS

A value of 4 mm provided the best cutoff point to dichotomize mesorectal extension for predicting prognosis. The distance of mesorectal extension more than 4 mm is an important predictor for postoperative recurrence and an independent prognostic factor for recurrence-free survival. A subclassification based on a 4-mm cutoff point is needed for improving the TNM staging system. However, further prospective study is necessary to prove reproducibility and validity of the cutoff point.

ACKNOWLEDGMENT

The authors thank Dr Kenta Murotani, Department of Biostatistics, Kurume University Graduate School of Medicine, for statistical technical support.

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