Table 3. Postoperative urinary functions (more than 12 months after surgery)

Patient no.	Reconstruction	Voiding	VV (ml)	RV (ml)
1	CUA	Spontaneous, continence	350	0
2	CUA	Spontaneous, continence	250	0
3	CUA	Spontaneous, continence	300	20
4	CUA	Spontaneous, continence	150	15
5	CS	Incontinence	Catheterization	
6	CS	Incontinence	Catheterization	
7	CS	Incontinence	Catheterization	
8	CUA	Spontaneous, continence	250	10
9	CS	Incontinence	Catheterization	

CUA, cysto-urethral anastomosis; VV, voided urine volume; RV, residual urine volume; CS, cystostomy

Table 4. Postoperative fecal evacuation functions (more than 12 months after surgery)

Patient no.	Continence	Stool frequency	Feces-flatus discrimination	Urgency	Soiling
2	(+)	3/day	Good	(–)	Night-time (–) Day-time (–)
4	(+)	3–5/day	Good	(±)	Night-time (–) Day-time (–)
8	(+)	5/day	Good–Fair	(±)	Night-time (±) Day-time (–)

at night was occasionally experienced during the first year postoperatively, but this improved in the second year. Excretory urography demonstrated excellent urinary function bilaterally with no evidence of hydronephrosis. Retrograde cystography did not show reflux in any of the five patients (Fig. 2). The four patients who underwent catheter-cystostomy passed urine via an inserted catheter. This voiding style was similar to that of patients with an ileal conduit; however, no special outfits were needed after catheter-cystostomy. Unfortunately, erectile function was not able to be preserved in any of the patients.

Of the three patients who underwent ISR with radical prostatectomy, none experienced major soiling or incontinence, although one patient suffered occasional minor soiling for about 1 year after closure of the diverting stoma. These patients passed fewer than five bowel movements per day and could discriminate feces from flatus by 1 year after stoma closure (Table 4). Anal function tended to improve slowly during the second year after surgery. Stoma closure is planned for the remaining patient.

Discussion

Locally advanced rectal cancer with adherence to, or involvement of the adjacent organs is not uncommon. En bloc excision of locally invasive rectal cancer without extrapelvic metastases can be curative, and TPE is still the conservative surgical option for locally advanced pelvic tumors, to achieve negative surgical margins in selected patients. This radical procedure was originally performed in the Ellis Fischel Cancer Center in the 1940s and was first reported by Brunschwig in 1948 as "a palliative operation for advanced cervical cancer"[23]. This formidable intervention carried with it high morbidity and mortality rates[5,6]. However, recent published series have reported mortality rates of lower than 10%, even with long-term follow-up[4,6,24,25]. Unfortunately, morbidity rates are still relatively high. TPE involving en bloc removal of the rectum, urinary bladder, distal ureters, and reproductive organs frequently requires diversion of urinary and anal functions, such as combined sigmoid colostomy and ileal conduit placement. TPE resulting in double stomas severely compromises the quality of life of these patients. Thus, orthotopic neobladder surgery is often attempted as an alternative for patients undergoing radical cystectoprostatectomy for bladder cancer, to enable voiding via the urethra with urinary continence[7,21]. Sphincter-preserving operations with coloanal anastomoses are also attempted for patients with distal rectal cancer.

We believe that even more limited excision is feasible and preferable if the tumor can be removed en bloc. In patients with locally advanced rectal cancer and invasion limited to the prostate or seminal vesicles, extended

Fig. 2. Postoperative urogram findings in patients who underwent cystourethral anastomosis showed no evidence of hydronephrosis or reflux. Left Patient 1, 40 months after surgery. Excretory urography shows no hydronephrosis. Right Patient 4, 6 months after surgery. Retrograde cystogram demonstrates a relatively small capacity (about 280 ml) and no reflux

colorectal resection with partial preservation of the bladder and anal sphincter may be possible, provided cancer-free margins can be achieved. Balbay et al. wrote: "Bladder-sparing surgery to treat patients with locally invasive colorectal carcinoma provides good local control without sacrificing survival. Selected men in whom CT and intraoperative evaluation identifies only localized involvement of the prostate or seminal vesicle appear to be reasonable candidates for bladder-sparing procedures"[22]. These procedures without ISR were first reported by Campbell et al. in 1993. In their experience of two patients, en bloc excision yielded negative surgical margins with no evidence of local recurrence at 1-year follow-up examination, and the patients displayed satisfactory control of intestinal and voiding function[22,27]. Although no long-term follow-up evaluation was reported, if adequate surgical margins can be achieved without total cystectomy, local and distant failure rates will not be diminished by cystectomy and urinary diversion.

In the present series, negative surgical margins were obtained in all patients by using en bloc resection combined with radical prostatectomy, even in the three patients with local pelvic recurrence of colorectal cancer. No standards for the treatment of locally recurrent rectal cancer have been established. Local recurrence close to or involving nearby pelvic organs after APR often cannot be resected with negative margins unless TPE is performed. Fortunately, negative surgical margins were obtained by bladder-sparing surgery in these three patients with local recurrence involving the prostate or seminal vesicles, or both. Despite our concerns about the risk of local recurrence after limited excision to preserve the superior or inferior bladder vessels to supply the residual bladder, no local recurrence was seen during follow-up (median, 26 months). Moreover, the patients who underwent CUA reported satisfactory control of voiding function. Their voiding style was similar to that of patients with an ileal neobladder. Unfortunately, the remaining four patients required cystostomy after preservation of the membranous urethra was deemed impossible because of probable cancerous invasion. These patients voided via an inserted catheter without special outfits, much like patients with an ileal conduit. An obvious difference between neobladder surgery and bladder-sparing surgery is that the neobladder is made using intestine, which presents inevitable long-term complications such as mucinous production, nutritional abnormalities, metabolic acidosis, skeletal demineralization, and the risk of malignant transformation in the intestinal segment[27,29]. No such problems are associated with the bladder-sparing surgery we described because the original bladder is preserved.

Anal sphincter-preserving surgery using ISR or ultra LAR was performed in 4 of these 11 patients, 3 of whom reported satisfactory control of anal function, while the others reported occasional minor soiling and other functional disturbances such as urgency, fragmentation, and frequent bowel movements. In our experience, and that of other authors, curability and acceptable anal function can be achieved with ISR in patients with very low rectal tumors[12–17]. Attempts should be made to preserve the anal sphincter, partially or completely, whenever possible.

In this series, the bladder was preserved successfully in eight men, by performing prostatectomy without compromising local control, even though these patients had been considered candidates for standard TPE. Bladder-sparing surgery seems to be an appropriate procedure for patients with locally advanced colorectal cancer involving the prostate or seminal vesicles, or both, without urinary bladder invasion, extensive pelvic nodal metastasis, or distant metastasis. Exploration was necessary to determine if limited en bloc resection of invasive rectal cancer was feasible, since discrimination between cancerous involvement and inflammatory adhesions is very difficult intraoperatively, although preoperative imaging examinations such as CT, MRI and PET can be helpful. We recommend careful intraoperative examination using frozen sections to evaluate the extent of pelvic invasion, and to determine whether limited resection is possible. However, intraoperative decisions based on frozen sections may carry some risk, since tumor exposure can occur and convert a potentially curative resection into a noncurative resection. However, if the bladder and anal sphincter are spared, the procedures described offer several advantages over TPE. We think that these procedures may yield improved functional results without compromising local control. More experience and longer follow-up evaluations are necessary to define the operative morbidity, risk of recurrence, and functional results associated with these surgical procedures.

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特集

超低位直腸癌における肛門括約筋部分温存手術の適応と方法

Partial and sphincter-preserving operation in patients with very low rectal cancer

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●要旨●外科的肛門管に及ぶ肛門にきわめて近い超低位進行直腸癌の標準手術は，腹会陰式直腸切断術である。

しかし最近では，内肛門括約筋の切除を主とする肛門括約筋部分温存手術により，直腸切断術の回避が可能とされる報告も認められるようになった。本稿では肛門括約筋部分温存術の適応と，その実際の手術手技について要点を解説した。また本手術法による長期成績は未だ不明な点もあるため，本法を実施するにあたり相当な慎重さが要求されることも述べた。

● key words：外科的肛門管，直腸切断術，肛門括約筋部分温存手術，内肛門括約筋，外肛門括約筋

はじめに

近年の下部直腸癌の手術では，手術手技や機器の発達により肛門温存術が増加している。しかし，外科的肛門管やその近傍の超低位直腸癌症例では，腹会陰式直腸切断術（APR）が標準手術法であり永久人工肛門が必要となる。この理由として，①この部位の癌では坐骨直腸窩や肛門挙筋に沿うリンパ節転移の可能性，②肛門温存が手技的にきわめて困難であること，③肛門括約筋切除により排便機能が廃絶する可能性が大変に大きいこと，などがあげられていたためである。しかし最近では，肛門にきわめて近い超低位直腸癌（肛門縁から腫瘍の下縁が5 cm以内に存在する）に対し，外肛門括約筋を可能な限り温存しながら内肛門括約筋を切除する手術（intersphincteric resection：ISR）が臨床応用されるようになり，その結果が報告されている[1-9]。これまでの報告によると，①の項目については否定的であり[1-3]，また③の術後排便機能はさまざまな排便障害は存在するものの容認できる結果であるとされている。

また腫瘍学的な予後も，比較的良好な結果が得られている。そこで本稿では，当施設で実施しているISRとこれに加えた外肛門括約筋部分合併切除（partial external sphincteric resection：PESR）などの肛門括約筋部分温存手術の適応と方法について述べることにする。

肛門管の局所解剖と各手術法の切除線

1. 局所解剖

肛門括約筋部分温存手術を行うにあたって，肛門管の解剖に精通することが重要となる。肛門管の局所解剖についてはすでに報告しているため[10-16]，ここでは簡単に述べることにする（図1）。解剖学的肛門管は肛門縁（anal verge：AV）から歯状線（dentate line：DL）までであるが，臨床的に取り扱う肛門管は実際に狭くなった部分の全体を外科的肛門管（平均3～5 cm）として呼んでいる。肛門から手指を挿入した場合，AVから約1 cm程度の部位に輪状の浅い陥凹を示す溝が存在し，これは内肛門括約筋の終末部と外肛門括約筋皮下部の内側上縁の境界に相当する括約筋間溝（intersphincteric groove：ISG）である。

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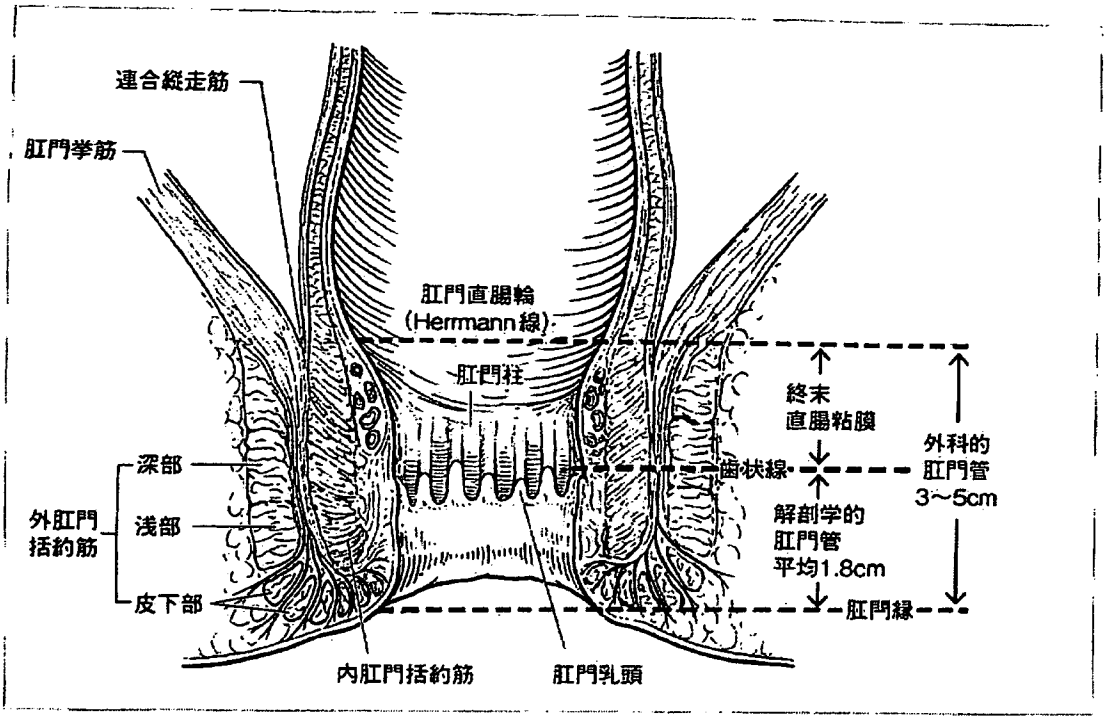


図1　肛門管の構造

この口側は狭い管状部となり，これを通過するとドーム状の広い部位となる。ここが肛門直腸輪（恥骨直腸筋付着部上縁）で，ほぼHerrmann線と一致する。直腸の内輪状筋はこの部位付近より肥厚を始めISGで終末となり，これが内肛門括約筋（internal sphincter：IS）で平滑筋である。外肛門括約筋（external sphincter：ES）は肛門管外側を筒状に取り巻く横紋筋であり，皮下部，浅部，深部から構成され，肛門管の持続的閉鎖作用を有する。内外肛門括約筋の間には疎な組織として認識される連合縦走筋（conjoined longitudinal muscle：CLM）が存在し，これは直腸の縦走筋と肛門挙筋の一部が融合して放射状に分岐して広がる線維性筋組織である。肛門管は，このように大切な機能を有する筋組織によって包まれている。

2. 各術式の切除線（図2）

APRの回避を目的とした当施設における肛門括約筋部分温存手術は内肛門括約筋の切除線により a total intersphincteric resection（total ISR），b subtotal ISR，c partial ISR，d各ISRに種々のpartial external sphincteric resection（PESR）を加えたもの（ISR＋PESR）に大別される。PESRはさらに細かく分類されるが，本稿では省略することにする。各術式の切除線を図2に示すが，これらの各術式の選択は腫瘍の肛門側下縁の位置と腫瘍浸潤の最深部の部位で決定される。つまり，distal marginとradial marginをどこの部位に設定するかにより決定されるものである。これにはAV，ISG，DL，IS，CLM，ESなどと腫瘍の位置関係が重要となる。図3にAPR標本のルーペ像を示すが，この症例の場合はISRおよびISR＋PESRでも十分なsurgical marginsが得られることがわかる。本術式の適応については，次の項目で述べる。

各手術法の適応について

最初に肛門括約筋部分温存手術の適応について，その概要を表1に示す。原則的に腫瘍下縁がAVより1～5cm以内のType 1，2の腫瘍までの症例が原則であり，低分化型線癌とType 4は除外する。Type 3は要注意である。その他に年齢では75歳前後までとし，術前に正常範囲内の排便状態を有する症例としている。また本手術法は標準手術とは異なることを説明し，承諾の得られた症例に施行している。以下に各手術法の適応について述べる。

1. total ISR

連合縦走筋（CLM）内を剥離して外肛門括約筋を温存し，肛門側は括約筋間溝（ISG）で切除して内肛

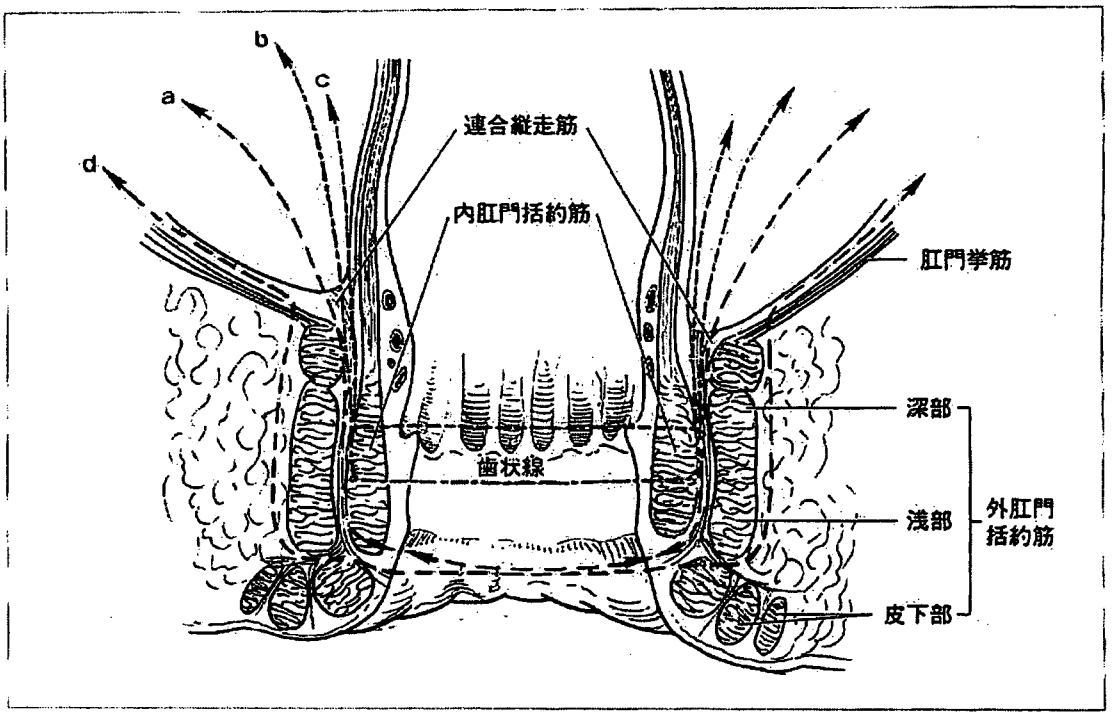
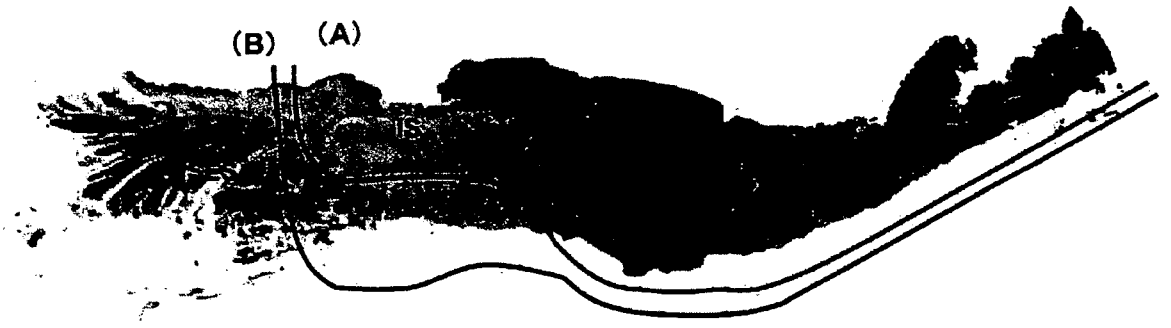


図2　術式分類
a：total ISR　b：subtotal ISR　c：partial ISR　d：total ISR＋PESR の例

(A)：ISR(Internal sphincteric resection)
(B)：ISR+PESR(Partial external sphincteric resection)

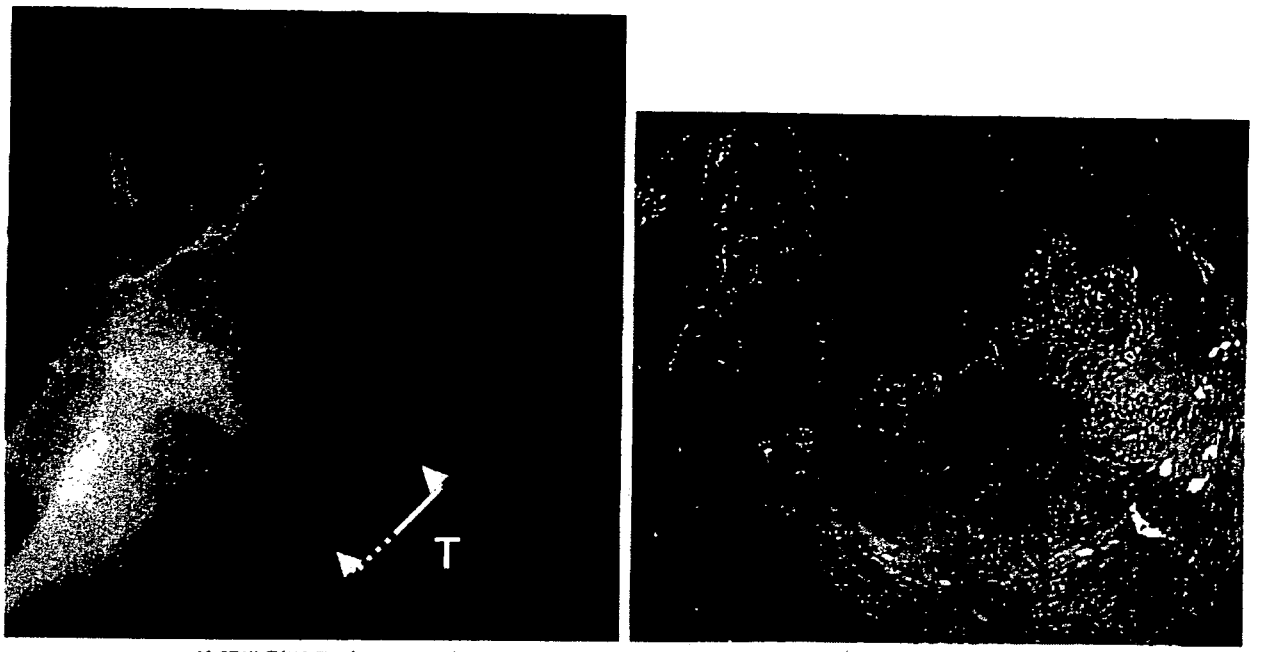


IS : Internal sphincter
SES : Subcutaneous part of external sphincter

図3　APR 標本を用いた括約筋部分温存手術の切除線

表1　肛門括約筋部分温存手術の適応

Location	
	anal verge（AV）より5cm以内の腫瘍で，下縁がAVより10mm以上口側に存在
Tumor Stage	
	主にT3までで，一部のT4を含む
Type	
	Type1，Type2でType3は要注意，Type4は除外
その他	
	P/D，mucinous Ca.は除外することが多い
	Age―原則的に75歳前後まで
	正常範囲内の排便状態を有する
	ICで承諾が得られている



a：注腸造影所見（T；tumor）　　b：大腸内視鏡所見（直腸内反転像）

図4　症例1

門括約筋を全摘し，結腸肛門吻合を行う術式である。本法の適応は，外科的肛門管より口側で腫瘍がT3であってもよいが外科的肛門管に及ぶ腫瘍はT2までであり，肛門管に存在する腫瘍下縁が歯状線（DL）およびその直上に及ぶ症例である。

2. subtotal ISR

本法は内肛門括約筋全摘とは異なり，肛門側の内肛門括約筋の一部を温存する術式であり，肛門側切除線はDLとISGとの間に存在する。本法の適応は，肛門管内の腫瘍下縁がDLより口側1 cm以内に存在する場合である。他の条件は，total ISRの場合と同様である。

3. partial ISR

本法は内肛門括約筋の一部が切除される術式であり，肛門側切除線はDLの直上からその1 cm程度口側の間となる。本法の適応は，腫瘍下縁がDLより口側1 cm以上の肛門管から肛門管上縁の間に存在する場合である。その他の条件は，totalおよびsubtotal ISRの場合と同様である。本法には，従来から行われていた結腸肛門吻合（いわゆるCAA）が一部含まれることになる。

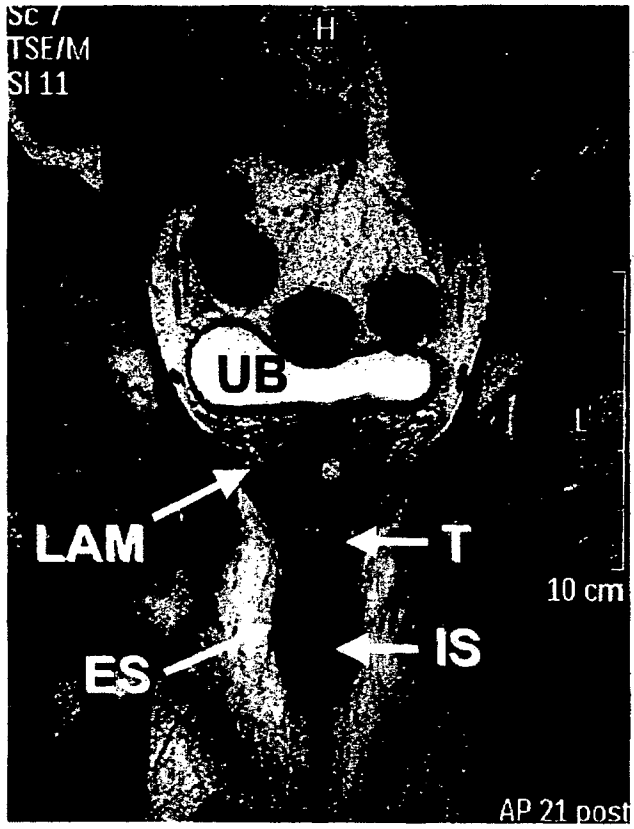
4. ISR＋PESR

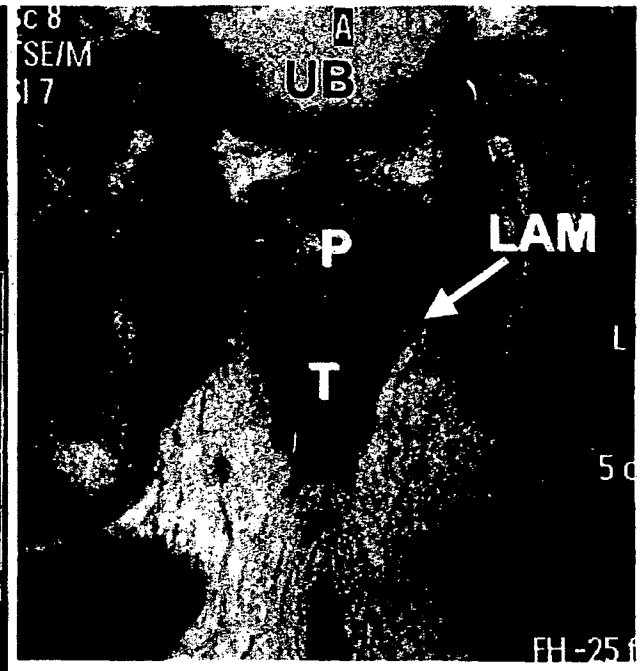
本術式では，内肛門括約筋と外肛門括約筋の皮下部を除く部分的な外肛門括約筋が一緒に切除される。したがって，さまざまな程度の外肛門括約筋が温存（皮下部は全温存）される。この術式では，内肛門括約筋に対してはtotal ISRとなることが多い。しかし，腫瘍下縁の位置により，内肛門括約筋の一部が温存される場合もある。腫瘍の最深部が，肛門管のどの部位に存在するかにより異なるわけである。つまり肛門管内で腫瘍がT3またはT4（外肛門括約筋に浸潤）となる部位で大きく異なるわけであり，また前述した腫瘍の下縁の位置で異なることになる。

上述した各術式の選択にあたり，術前および術中における腫瘍の浸潤度診断が重要となる。術前では直腸指診や内視鏡による腫瘍下縁の位置の計測と判定が，また直腸肛門管MRI画像による浸潤度診断などがきわめて重要である。注腸造影所見のみでは，肛門管の十分な描出が不可能なこともあり不十分である。以下に症例を提示する。

〈症例1〉

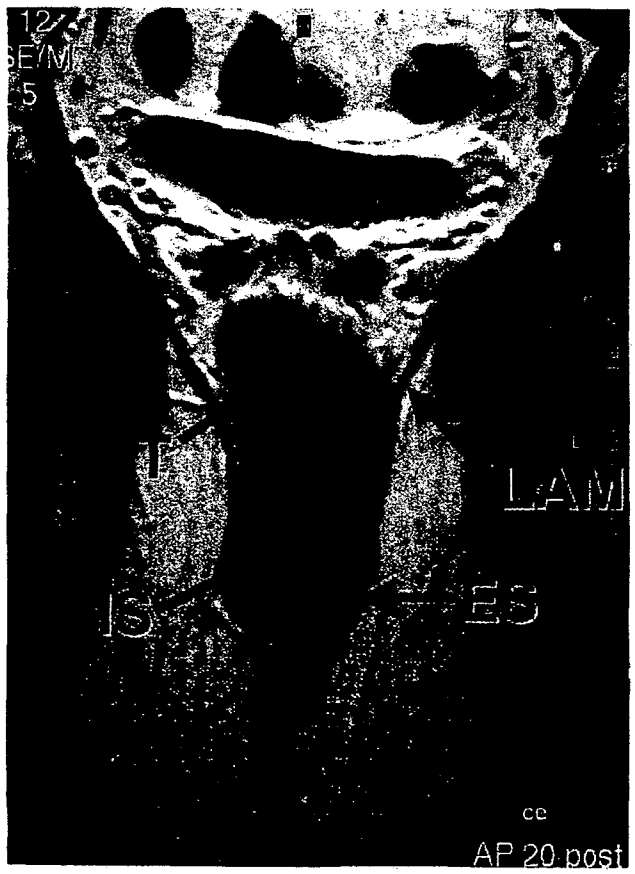
図4は56歳，男性の注腸造影像と内視鏡像であり，注腸像では腫瘍下縁の部位と肛門管の関係の把握が難しい。内視鏡と直腸指診による計測で，Type 2の腫瘍の下縁はAVより4 cmであった。図5に本症例のMRI画像を示す。腫瘍と内・外肛門括約筋および肛門挙筋の関係が描出され，腫瘍の浸潤範囲は内肛門括約筋内であり，肛門挙筋および外肛門括約筋には浸潤

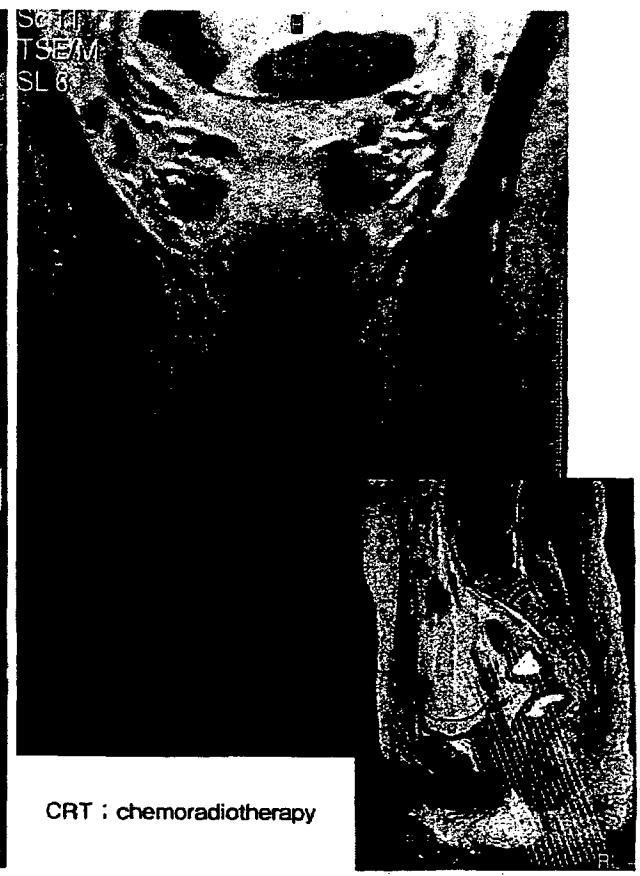




UB：urinary bladder
LAM：levator ani muscle
IS：internal sphincter
ES：external sphincter
P：prostate

図5　症例1：MRI所見





CRT：chemoradiotherapy

a：pre-CRT　　b：post-CRT

図6　症例2：MRI所見

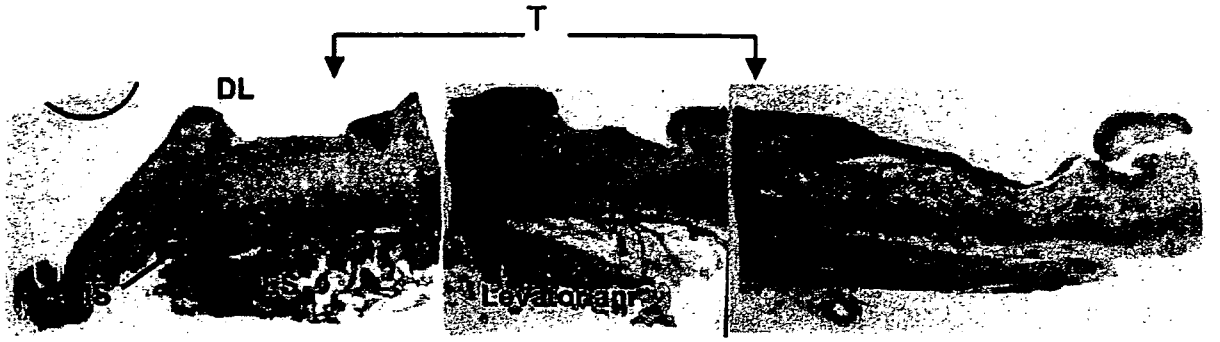


図7　切除標本のルーペ像（total ISR + PESR 例，症例2）
location：anorectal junction
size：23×23mm
TNM：pT2，pN0，M0
histologic type：moderately differentiated adenocarcinoma
lymphatic invasion：none
venous invasion：low-grade
surgical margins：cancer-free（negative）
：circumferential：7mm
：distal；15mm
DL：dentate line　IS：internal sphincter　ES：external sphincter　T：tumor

所見を認めない。本症例の術式は，partial もしくは subtotal ISR で十分な根治的切除が可能と考えられる。

〈症例2〉

図6は症例2の MRI 画像である。術前放射線化学療法（CRT）前および後の画像であり，左の CRT 後の所見では腫瘍左側で LAM および ES の一部と腫瘍との境界がはっきりしない。このため本症例では total ISR + PESR（左側）が施行された。本症例の切除標本ルーペ像を図7に示すが，腫瘍は ES に浸潤所見を認めず，十分過ぎる surgical margin が得られている。これは術前補助療法による変性のため，正確な浸潤度診断が困難であったためである。このような過大手術に対しても，注意を要する。

手術の実際

実際の本手術法の要点について表2に示すが，以下に簡単に述べる。

1. 腹腔操作

通常の低位前方切除術に準じて行う。下腸間膜動脈の切離は，吻合に用いる結腸の良好な血流を確保するために可能な限り左結腸動脈（LCA）を温存する。吻合時に結腸の緊張が問題となる場合，LCA を犠牲にする。

表2　手術の実際

腹腔側～骨盤内操作
・LCA 温存 ・TME ・肛門管剝離 ・側方リンパ節郭清またはサンプリング ・自律神経温存
肛門側操作
・肛門管・直腸内の洗浄 ・切除側断端の閉鎖 ・標本切除 ・結腸・肛門吻合
一時的人工肛門造設
一時的人工肛門閉鎖（3カ月以降）

2. 骨盤内操作

超低位前方切除の場合と同様に，total mesorectal excision（TME）を十分に行う。その後に外科的肛門管の剝離を行うのであるが，図8のごとく肛門挙筋群が直腸・肛門管を取り巻く部位を十分に認識し，慎重に肛門側へ剝離を行い肛門側へ可能な限りすすめる。腫瘍の浸潤度により剝離（切離）線が異なり，ISR の場合は内外括約筋内の CLM の層で剝離を行う。

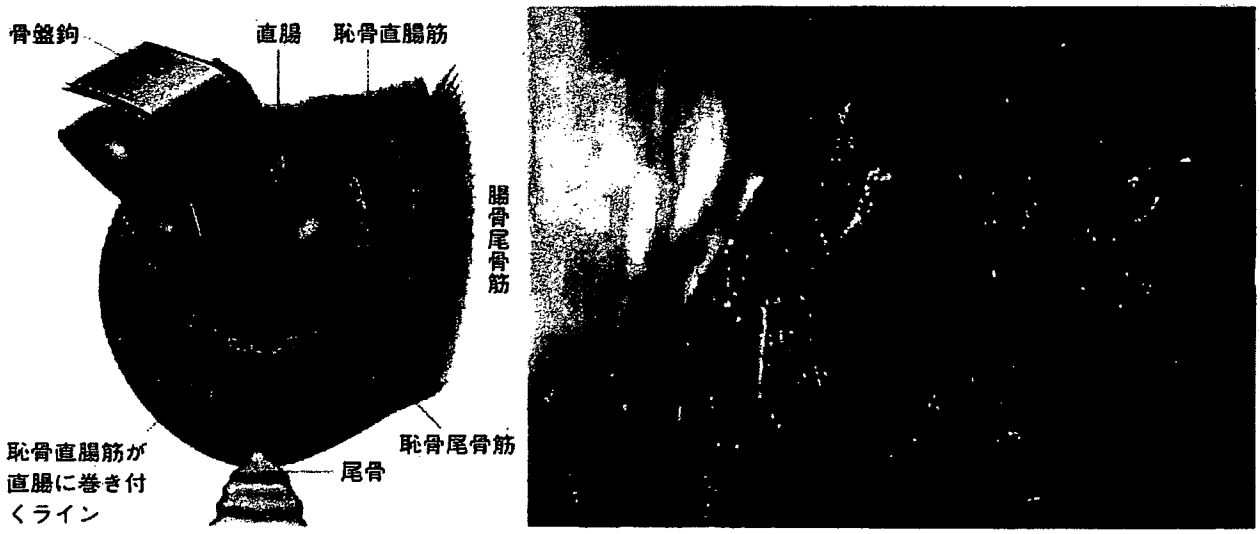
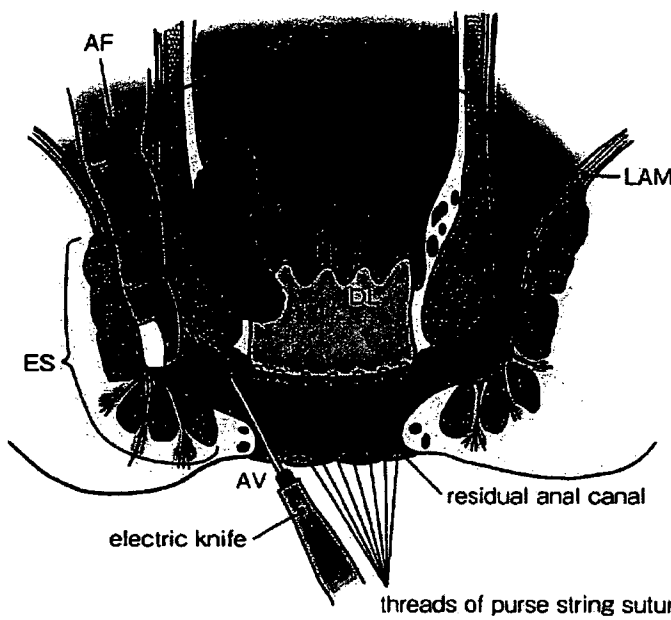


図8　骨盤底から肛門側への剝離



AF：assistant's finger-tips
T：tumor
ES：external sphincter
IS：internal sphincter
DL：dentate line
LAM：levator ani muscle
AV：anal verge

図9　肛門側操作

PESRの場合は癌の最深部の部位により異なるが，合併切除する外肛門括約筋の部位の外側に切離線を設定して切り込む。これらの操作の終了後に，自律神経を温存しながら側方郭清を実施する。

3．肛門側操作

最初の肛門側操作は，肛門管・直腸内の十分な洗浄（2l以上）である。このときの腸管のクランプは，当然のことながら腫瘍の口側となる。洗浄後に開肛器を用いて肛門管の展開を行い，腫瘍下縁とAVを確認して肛門側切除線の設定を行う。distal marginをどの位確保するかにより，total，subtotal，partial ISRが決定される。各部位で内肛門括約筋を全周に切離しながら，切除側肛門管断端を縫合閉鎖し，糸は支持糸として残す（図9）。この操作により切除標本が摘出される。骨盤腔内から肛門に向かって十分に洗浄した後，口側結腸を肛門へ引き出して3－0吸収糸で結腸・肛門管（肛門）吻合を全層で行う（平均20～24針程度）（図10）。なお，切離端の迅速病理検索でcancer-freeでない場合は，APRに変更することを考慮する。

図10　結腸肛門吻合終了時

表3　根治的肛門括約筋部分温存術の症例

	Nov. 1999～Dec. 2006		NCCHE
no. of patients	: 132		
gender	: male 97, female 35		
age, median (range ; yr)	: 57 (27～80)		
distance to AV, median (range ; cm)	: 3.7 (1.5～5.0)		
surgical procedure	: total ISR	: 23	38 → APR : 1, Hartmann : 2
	total ISR with PESR	: 15	
	subtotal ISR	: 59	
	partial ISR	: 35	
neoadjuvant therapy (45Gy, 5-Fu)	: 48		

follow-up period : 36 months, median (range : 3～74months)

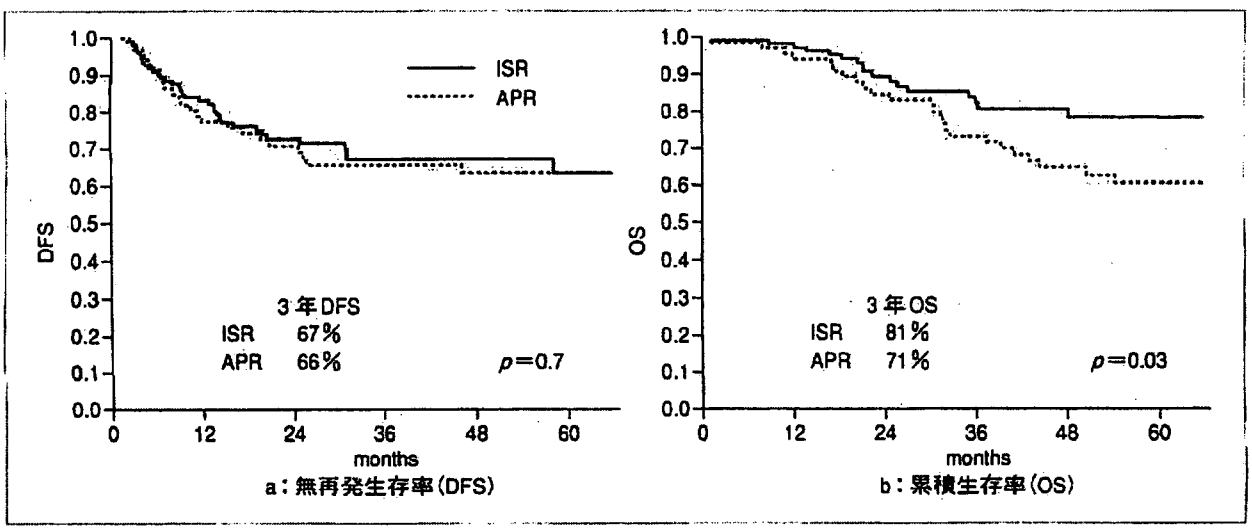


図11　予後 (ISR vs APR)
median follow-up : ISR 1082日, APR1450日

4. diverting stoma造設，ドレーンの留置

肛門側操作の終了後，diverting stoma（回腸または横行結腸）の造設を行う。骨盤腔内に2本のドレーンを後腹膜経路で留置し，後腹膜を修復した後に閉腹して手術を終了する。diverting stomaの閉鎖は，3カ月以後に行っている。

おわりに

本稿で述べた肛門括約筋部分温存手術により，大半の下部直腸癌症例で直腸切断術は回避可能である。当施設では2006年12月までに，根治的な本手術法を132例に施行した（表3）。手術関連合併症はやや多く，20～30％に認められた。その中間成績において，腫瘍学的予後はAPRに劣らないこと（図11），多くは許容範囲内であるが種々の程度の排便機能障害が確かに存在すること，などが判明している。また再発は肺転移再発がもっとも多く，surgical marginsからの再発は少ないことも判明している。しかし，長期の腫瘍学的および排便機能の予後，その他についてはまだ十分な結果が得られていないのが実情である。このため本法は，まだ標準術式にはなっていない。現在，本法の多施設共同臨床試験（厚生労働省がん研究助成金研究，および大腸癌研究会プロジェクト研究）が進行中であり，その結果が待たれるところである。以上のことより，手術手技の複雑さ，合併症や排便機能障害も考慮し，本法の実施には十分な慎重さが要求される。

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Original Paper

Clinicopathological Features of Skip Metastasis in Colorectal Cancer

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ABSTRACT

Background/Aims: Japanese general rules for the staging of colorectal cancer conventionally classify lymph node metastasis into three groups according to location with respect to the primary tumor. Skip metastasis, in which distant nodes are positive but regional nodes are negative, is often encountered but poorly understood. We studied the clinicopathological features of skip metastasis in colorectal cancer.

Methodology: The location of positive nodes was classified in 323 patients with Dukes' stage C colorectal cancer. Skip n2 lymph node metastasis was defined as positive N2 metastasis without negative N1 or N3 metastasis. Clinicopathological findings and survival were compared between the patients with skip n2 metastasis (skip n2 group) and those with n1 (n1 group) or n2 metastasis (n2 group).

Results: There were 211 patients in the n1 group, 91 in the n2 group, and 21 in the skip n2 group. Pathological examination showed that the skip n2 group had fewer positive nodes than the n1 and n2 groups, but was positioned between these groups with respect to the degree of lymphatic invasion. Cumulative survival was significantly poorer in the n2 group than in the skip n2 group ($p=0.039$ by log-rank test). Survival was similar in the skip n2 group and n1 group. There was also no difference in survival between patients in the skip n2 group and patients with one, two, or three N1 metastases.

Conclusions: Lymph nodes with skip n2 metastasis are most likely sentinel nodes of the primary tumor in patients with colorectal cancer. The prognosis of patients with skip n2 metastasis is therefore better than that of patients with n2 metastasis and similar to that of patients with n1 metastasis.

KEY WORDS: Skip metastasis; Colorectal cancer; Lymph node metastasis

ABBREVIATIONS: Hematoxylin and Eosin (HE)

INTRODUCTION

Although various prognostic factors have been proposed in colorectal cancer, lymph node metastasis and the depth of tumor invasion remain the most reliable predictors of outcome. The presence of lymph node metastasis has been used in many staging systems since the establishment of Dukes' classification (1). The numbers or locations of lymph node metastases are included as staging factors for lymph node metastasis in Dukes' stage C disease (2-5).

In Japan, lymph node metastasis is classified according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (6). Information on the number of positive nodes and the location of lymph node metastasis is thereby provided. Skip metastasis, in which distant nodes are positive but regional nodes are negative, is often encountered but poorly understood. The presence of skip metastasis can increase the risks associated with laparoscopic surgery or other minimally invasive procedures. Failure to diagnosis skip metastasis can also lead to selection of ineffective regimens for chemotherapy. To gain a better understanding of the status and implications of skip metastasis, we studied the clinicopathological features of skip metastasis in patients with Dukes' stage C colorectal cancer.

METHODOLOGY

Patients and Methods

From February 1990 through August 2002, we studied 323 patients with Dukes' stage C colorectal cancer who underwent curative resection at Kanagawa Cancer Center. Patients with multiple advanced cancers or mucinous or signet-ring-cell carcinomas were excluded.

During operation, the distance from the tumor margin was measured and marked on the mesentery at 5-cm intervals to determine lymph-node location. The mesentery was separated from the resected specimen and fixed in 10% formalin solution. All removed lymph nodes were embedded in paraffin, stained with hematoxylin and eosin (HE), and examined histopathologically to determine metastatic status. The resected nodes were histologically examined by two pathologists. We evaluated the numbers of positive nodes and the locations of lymph node metastases and classified

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TABLE 1 The Number of Cases with Skipping Nodal Metastasis of n2 according to the Location of the Tumor

	Location	n1	Skip n2	n2	Total cases	Skip %
Colon	Cecum	7	1	4	12	8.3%
	Ascending	24	1	9	34	2.9%
	Transverse	14	1	3	18	5.6%
	Descending	10	2	4	16	12.5%
	Sigmoid	63	5	26	94	5.3%
Rectum	Rectosigmoid	35	1	10	46	2.2%
	Rectum above peritoneal reflection	17	5	7	29	17.2%
	Rectum below peritoneal reflection	39	5	27	71	7.0%

TABLE 2 Number of the Cases in Three Directions of the Skip n2 Metastasis according to the Location of the Tumor

	Location	Main nodes	Paracolorectal nodes	Lateral nodes	Total cases
Colon	Cecum	1			1
	Ascending	1			1
	Transverse		1		1
	Descending	1	1		2
	Sigmoid	5			5
Rectum	Rectosigmoid	1			1
	Rectum above peritoneal reflection	5			5
	Rectum below peritoneal reflection	3		2	5
		17	2	2	21

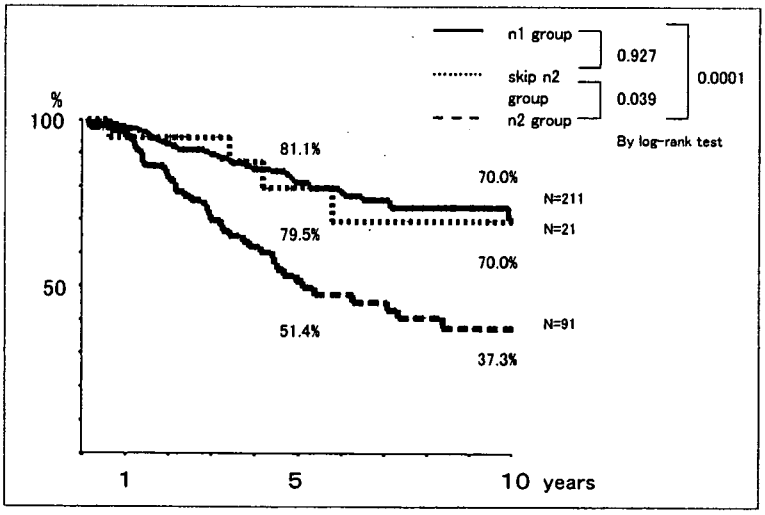

FIGURE 1 Overall survival rates of patients with n1, skip n2, and n2 lymph nodes metastasis.

positive nodes as n1, n2, and n3 according to the Japanese General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (6).

The Japanese rules propose that colon cancer has two directions of lymph nodes metastasis: along the axis of the bowel (paracolic nodes) and along the origin of the main vessel supplying the primary tumor site (main nodes). Rectal cancer has three types of lymph node metastasis: paracolic nodes, main nodes, and lateral pelvic nodes along the internal and external iliac arteries. The paracolorectal nodes located within 5cm from the tumor margin are classified as N1 nodes, and those between 5 and 10cm from the tumor margin are classified as N2 nodes. The N2 nodes also include the main nodes, with the exception of the N3 nodes, around the origin of the main vessel. The patients were classified as having n1, n2, or n3 lymph node metastasis according to the level of the most distant, microscopically positive nodes. These categories are defined as follows: n1 metastasis means positive nodes only in the N1 region; n2 metastasis indicates positive nodes in the N1 and N2 regions and negative nodes in the N3 region; and skip n2 metastasis means positive nodes in the N2 region, but negative nodes in the N1 and N3 regions. In addition, cases with positive lateral pelvic nodes, but negative paracolorectal nodes and main nodes were also considered positive for skip n2 metastasis.

Clinicopathological findings and survival were compared between the skip n2 group and the n1 or n2 group. The chi-square test and unpaired *t*-test were used for statistical analysis of two unpaired samples. Cumulative 5-year survival rates were calculated by the Kaplan-Meier method. The log-rank test was used to compare survival curves. All tests were two-tailed, and $p<0.05$ was considered to indicate statistical significance.

RESULTS

The 323 patients with Dukes' stage C disease were classified according to the location of positive nodes. There were 211 patients in the n1 group and 91 in the n2 group, as compared with only 21 in the skip n2 group.

Skip n2 metastasis was most commonly associated with primary tumors arising in the descending colon and upper rectum as compared with other portions of the colorectum (**Table 1**). The direction of skip n2 metastasis with respect to the location of the primary tumor was mainly along the main nodes (**Table 2**). Two of five cases (40%) of lower rectal cancer had skip metastasis to the lateral pelvic nodes.

Clinicopathological examination (**Table 3**) showed that the frequency of well-differentiated adenocarcinoma was higher in the skip n2 group than in the n1 or n2 groups. The degree of lymphatic invasion in the skip n2 group was intermediate between those in the n1 and n2 groups. Other clinicopathological findings did not differ significantly among the three groups.

The mean number of positive nodes in the skip n2 group was significantly lower than those in the n1 and n2 group (**Table 4**).

Cumulative survival was significantly poorer in the n2 group than in the skip n2 group ($p=0.039$ by log-rank test). Survival was similar in the skip n2 group and n1 group (**Figure 1**). There was also no difference in survival between the skip n2 group and patients with one, two, or three N1 metastases (**Figure 2**).

TABLE 3 Clinicopathological Features of the Three Groups

		n1 group	skip n2 group	n2 group	*P* value
Gender	male	118	12	58	0.448
	female	93	9	33	
Age		62.0 0.8	66.6±1.8	62.7±1.2	ns***
Diameter	(mm)	47.1±1.3	49.0±2.7	51.3±1.9	ns***
Histological type[a]	wel	65	10	14	
	mod	129	11	69	0.010
	por	17	0	8	
Macroscopic type	1	31	4	9	
	2	146	12	60	
	3	26	5	17	0.414
	4	8	0	5	
Depth of invasion	11	9	1	0	
	12	19	2	5	
	13	108	10	42	0.003
	14	75	8	44	
Iy[b]	0	49	5	14	
	1	129	12	45	
	2	27	3	24	0.011
	3	6	0	8	
V[c]	0	87	9	27	
	1	65	5	32	
	2	49	7	27	0.435
	3	9	0	5	

ns*** ; there were no significance between n1, skip n2 and n2 groups.
[a] Histological type-wel: well differentiated adenocarcinoma; mod: moderately differentiated adenocarcinoma; por: poorly differentiated adenocarcinoma.
[b]ly: lymphatic invasion were classified with degree of amounts of tumor invasion.
[c]v: venous invasion were classified with degree of amounts of tumor invasion.

DISCUSSION

Our study showed that skip n2 metastasis was less common than n1 and n2 metastases. The degree of lymphatic invasion associated with skip n2 metastasis was intermediate between that of n1 and n2 metastases, suggesting that implantation of tumor cells in distant lymph nodes requires a high degree of lymphatic invasion.

Recently, many investigators have reported that sentinel node mapping is useful for staging colorectal cancer (7-9). Marrie *et al.* (10) found that direct lymphatic drainage to apical anatomic skip lesions occurred in 15% of 26 colon cancers evaluated by keratin 20 reverse transcription polymerase chain reaction. Saha *et al.* (11) reported skip metastasis in 3.9% of colorectal cancers on hematoxylin and eosin staining. The incidence of skip metastasis in colorectal cancer as assessed by molecular techniques is estimated to be higher than previously estimated (8).

Our study also demonstrated that the survival of patients with skip n2 metastasis was similar to that of patients with one, two, or three N1 metastases. Moreover, the mean number of positive nodes in the skip n2 group was significantly lower than that in the n1 and n2 groups. This finding suggests that most lymph nodes with skip metastasis are sentinel nodes. Lymph node mapping is therefore useful for detecting lymph nodes with skip metastasis and can help to ensure that metastatic lymph nodes are completely resected along with the primary tumor.

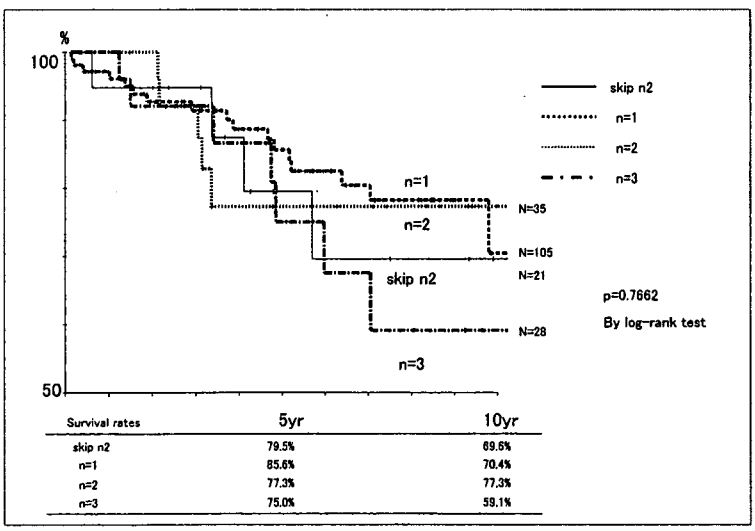

FIGURE 2 Overall survival rates of patients with one, two, three lymph node metastasis in N1 area and skip n2 lymph node metastasis.

Yamamoto *et al.* (12) found that the presence of skip metastasis is associated with better outcomes than the absence of skip metastasis in patients with colorectal cancer. Shida *et al.* (13) reported that 31.6% of patients with n2 colon cancer have skip metastasis, but

TABLE 4 Comparison of the Number of Lymph Nodes with Metastasis

	Total number of dissected lymph		Number of n1 lymph		Number of n2 lymph nodes with metastasis		Total number of lymph nodes with metastasis	
n1 group	29.7±1.2		2.5±0.2		0		2.5±0.2	
		P=0.489						P=0.036
skip n2 group	26.9±3.2	P=0.628	0	P<0.001	1.2±0.1	P=0.010	1.3±0.1	P<0.001
		P=0.596						P<0.001
n2 group	28.7±1.4		4.2±0.4		2.5±0.2		6.8±0.5	

(Mean±SE)

found no significant difference between patients with skip metastasis and those without skip metastasis. We found that the outcome of patients with skip n2 metastasis was similar to that of patients with n1 metastasis, but better than that of patients with n2 metastasis. This finding justifies the staging of colorectal cancer according to the number of lymph node metastases, as done in the TNM classification (14). However, an anatomical assessment of lymph node metastasis is useful for deciding the required extent of mesenteric lymph node resection. Moreover, the possibility of skip metastasis should be considered in patients undergoing curative resection for colorectal cancer.

Our results suggest that both the locations and the numbers of lymph node metastases should be incorporated into classification systems for the evaluation of patient prognosis.

In summary, our clinicopathological study showed that n2 skip metastasis was less common than n1 or n2 metastasis. The degree of lymphatic invasion associated with n2 skip metastasis was intermediate between that associated with n1 metastasis and that associated with n2 metastasis. Lymph nodes with skip metastasis were apparently sentinel nodes of the primary tumor. Therefore, the outcome of patients with skip n2 metastasis was similar to that of patients with n1 metastasis, but better than that of patients with n2 metastasis.

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Original Paper

Lateral Lymph Node Dissection for Lower Rectal Cancer

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KEY WORDS: Lateral lymph node dissection; Lower rectal cancer

ABBREVIATIONS: Lymph Node Dissection (LLD)

ABSTRACT

Background/Aims: This study was conducted to evaluate the effects of lateral lymph node dissection (LLD) on overall survival, disease-free survival, and local recurrence for the patients with lower rectal cancer.

Methodology: From 1990 through 2000, 169 consecutive patients with T2 (TNM classification) or more advanced, extended lower rectal cancer (located below the peritoneal reflection) underwent curative resection at Kanagawa Cancer Center were reviewed.

One hundred and forty-three patients who underwent LLD and the 26 patients who did not were entered in this study.

Results: Cox's multivariate regression analysis showed T stage (TMN classification), N stage (TNM classification), and LLD were found to be significantly related to the rates of both cumulative survival and disease-free survival. That mean LLD was identified as a significant prognostic factor. But disease-free survival did not differ significantly between the patients who underwent LLD and those who did not undergo LLD in stage I, II, or III disease ($p=0.3681$, $p=0.1815$, and $p=0.0896$, respectively).

The local recurrence rate was similar in patients who received LLD (17.5 percent) and in those who did not receive LLD (23.1 percent; $p=0.498$). But 7 patients with lateral lymph node metastasis (33.3 percent) remained disease free. And these patients had local lateral lymph node metastasis and benefited from LLD.

Conclusions: LLD can substantially improve outcomes in selected patients at high risk for lateral lymph node metastasis. A randomized controlled clinical study is necessary to clarify the role of LLD in the treatment of rectal cancer.

INTRODUCTION

In lower rectal cancer, lymphatic drainage is mainly to the superior rectal artery and inferior mesenteric artery or to the lateral lymph nodes beyond the pelvic nerve plexus (1-3). Lymph node metastasis most frequently occurs along the inferior mesenteric artery, and patients with lateral node metastasis have a poor prognosis (4-6). Lateral lymph node dissection (LLD) has therefore received considerable attention.

In Japan, extended lymphadenectomy has been done to improve outcome in rectal cancer (7-9), but complications associated with auto-nerve resection, such as urinary dysfunction and sexual disturbance, became evident with improved survival (7,10). Subsequently, surgeons in Japan developed a procedure for LLD with auto-nerve preservation (4,11-15). This procedure has improved urinary function, but sexual function remains unsatisfactory (4,11). Lateral lymph node metastasis has been considered systemic disease in patients with rectal cancer (16). However, some patients have only lateral lymph node metastasis, and the lateral lymph nodes have been designated regional lymph nodes (6,17,18). Such patients have had good outcomes after LLD. Available evidence thus suggests that LLD should be avoided in patients with a low risk of lateral lymph node metastasis or those unlikely to benefit from the procedure, thereby enhancing their postoperative quality of life. On the other hand, LLD should be done patients likely to benefit from the procedure in terms of a lower risk of local recurrence and an improved outcome. In this retrospective study, we evaluated the effects of LLD on overall survival, disease-free survival, and local recurrence.

METHODOLOGY

From 1990 through 2000, 169 consecutive patients with T2 (TNM classification) or more advanced, extended lower rectal cancer (located below the peritoneal reflection) underwent curative resection at Kanagawa Cancer Center. The diagnosis of depth of tumor invasion was due to barium enema, computed tomography, and colonoscopy. Because liver metastasis, peritoneal dissemination, and distant metastasis were considered to have a far stronger impact on outcome than LLD, patients with these conditions were excluded from analysis. Histopathologically, well, moderately, and poorly differentiated adenocarcinomas and mucinous adenocarcinomas were studied.

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Clinicopathological data was obtained from clinical chart, retrospectively.

The indication for LLD was originally T2 or more advanced, extended lower rectal cancer. We performed LLD with auto-nerve preservation. This procedure was contained total mesorectal resection. LLD was not done in patients who had cardiovascular complications or respiratory dysfunction, elderly patients, and those not consenting to the procedure. Patients were followed up by computed tomography and measurement of serum tumor makers (CEA and CA19-9) at intervals of 2 to 4 months for the first 2 years and 4 to 6 months thereafter. Median follow-up was 5.6 months. Adjuvant chemotherapy was recommended in all patients, and received by only patients hoped. Radiotherapy was not given.

The statistical significance of differences between groups was evaluated with the chi-square test and *t*-test. Cumulative survival rate and disease-free survival rate were calculated by the Kaplan-Meier method, and survival curves were compared by the log-rank test. Cox's regression analysis was used for univariate and multivariate analyses. A p value of <0.05 was considered to indicate statistical significance.

RESULTS

Clinicopathological Features of the Patients and Related Factors

The clinicopathological features of the 143 patients who underwent LLD and the 26 patients who did not are shown in **Table 1**. Mean age ($p=0.008$) and preoperative complications ($p=0.008$) differed significantly between these groups.

The overall rates of cumulative survival and disease-free survival at 5 years were 73.3 percent and 61.5 percent, respectively **(Figure 1)**. Cox's univariate regression analysis showed that the cumulative survival rate was significantly related to macroscopic type, T stage (TMN classification), N stage (TNM classification), preoperative levels of CEA and CA19-9 in serum, and LLD **(Table 2)**. In addition to these factors, disease-free survival rate was significantly related to histological type and intraoperative lymph node metastasis **(Table 3)**. T stage (TMN classification), N stage (TNM classification), and LLD were found to be significantly related to the rates of both cumulative survival and disease-free survival **(Tables 4, 5)**. LLD was thus an important prognostic factor for both cumulative and disease-free survival.

Survival Rate of Patients Undergoing LLD and Those Not Undergoing LLD

The disease-free survival rate at 5 years was significantly higher in patients who underwent LLD (65.4 percent) than in those who did not undergo LLD (39.0 percent; $p=0.0182$) **(Figure 2)**. Disease-free survival did not differ significantly between the patients who underwent LLD and those who did not undergo LLD in stage I, II, or III disease ($p=0.3681$, $p=0.1815$, and $p=0.0896$, respectively) **(Figure 3)**.

TABLE 1 Clinicopathological Features of Patients

		LLD (N=143)	No LLD (N=26)	*P* value
Sex	male	102	17	
	female	41	9	0.541
Age (Mean±SE)		60.2±0.9	66.4±1.9	0.008
Macroscopic type	elevated	120	17	
	depressed	23	9	0.088
Tumor diameter (Mean±SE)		53.2±1.7	52.6±5.9	0.902
Pathological type	well	49	10	
	mod	81	14	0.909
	others	13	2	
Depth of invasion	pT2	37	9	
	pT3	91	14	0.613
	pT4	15	3	
Lymph node status	pN0	67	10	
	pN1	35	7	0.72
	pN2	41	9	
Pathological stage (TNM)	I	28	5	
	II	39	5	0.66
	III	76	16	
Adjuvant chemotherapy	(-)	61	16	0.075
	(+)	82	10	
Preoperative serum CEA	normal	115	21	
	high	28	5	0.967
Preoperative serum CA19-9	normal	115	19	
	high	28	7	0.395
Preoperative complications	(-)		112	14
	(+)	31	12	0.008

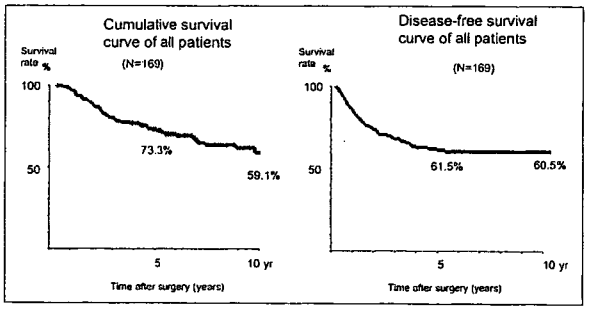

FIGURE 1 Mean observation period was 3390±146 (S.E.) days (95%CI: 3104-3675) after surgery for cumulative survival and 3098±157 (S.E.) days (95%CI:2790-3405) after surgery for disease-free survival.

Lateral Lymph Node Metastasis and Effect of LLD in Stage III Disease

The rate of disease-free survival 5 years after LLD did not differ significantly between patients with stage III disease who had lateral lymph node metastasis (33.3 percent) and those without lateral lymph node metastasis (47.4 percent). The rate of disease-free survival at 5 years was significantly higher in patients with stage III disease without lateral lymph node metastasis who underwent LLD (47.4 percent) than in patients with stage III disease who did not undergo LLD (25.0 percent; $p=0.0449$) **(Figure 4)**. Disease-free survival at 5 years was also analyzed after dividing the patients who underwent LLD into three groups: those without lateral lymph node metastasis, those with only one lateral lymph node metastasis, and those with two or more lateral lymph node metastases. There was no significant difference in disease-

free survival among these three groups. However, patients with one or more lateral lymph node metastases tended to have a poorer outcome than those without lateral lymph node metastasis (**Figure 5**).

Pattern of Recurrence With or Without LLD

The overall rate of recurrence was 34.3 percent in the patients who underwent LLD. Among these patients, the recurrence rate was 66.7 percent in patients with lateral lymph node metastasis and 28.7 percent in those without metastasis (p=0.001). The recurrence rate differed significantly between patients who underwent LLD (34.3 percent) and those who did not undergo LLD (57.7 percent) (p=0.023). The local recurrence was defined as intrapelvic recurrence except anastomotic one. The local recurrence rate was similar in patients who received LLD (17.5 percent) and in those who did not receive LLD (23.1 percent; p=0.498) (**Table 6**). The local recurrence rate in patients with lateral lymph node metastasis was 38.1 percent, as compared with 13.9 percent in patients without lateral lymph node metastasis (p=0.007).

Seven patients with lateral lymph node metastasis (33.3 percent) remained disease free. These patients had local lateral lymph node metastasis and benefited from LLD.

TABLE 2 Univariate Analysis of Prognostic Factors for Cumulative Survival

			Exp	C.I. 95%	*P* value
Sex	male	119	1.358	0.713-2.585	0.352
	female	50	1		
Macroscopic type	elevated	137	1		
	depressed	32	1.865	1.024-3.394	**0.041**
Pathological type	well	59	0.565	0.223-1.436	0.23
	mod	95	0.658	0.274-1.580	0.349
	others	15	1		
Depth of invasion	pT2	46	1		
	pT3	105	3.621	1.423-9.215	**0.007**
	pT4	18	10.065	3.460-29.277	**0.000**
Lymph node status	pN0	77	1		
	pN1	42	2.842	1.261-6.404	**0.012**
	pN2	50	7.079	3.436-14.588	**0.000**
Macroscopic lymph node metastasis	(-)	65	1		
	(+)	104	1.727	0.947-3.148	0.074
Adjuvant chemotherapy	(-)	77	1.065	0.619-1.833	0.821
	(+)	92	1		
Preoperative serum CEA	normal	136	1		
	high	33	1.946	1.054-3.592	**0.033**
Preoperative serum CA19-9	normal	134	1		
	high	35	2.18	1.211-3.925	**0.009**
Lateral lymph node dissection	(-)	26	2.342	1.271-4.317	**0.006**
	(+)	143	1		

TABLE 3 Univariate Analysis of Disease-free Survival

			Exp	C.I. 95%	*P* value
Sex	male	119	1.264	0.718-2.225	0.418
	female	50	1		
Macroscopic type	elevated	137	1		
	depressed	32	1.849	1.061-3.222	0.030
Pathological type	well	59	0.400	0.181-0.885	0.024
	mod	95	0.518	0.249-1.076	0.078
	others	15	1		
Depth of invasion	pT2	46	1		
	pT3	105	2.437	1.188-5.000	0.015
	pT4	18	5.334	2.241-12.696	0.000
Lymph node status	pN0	77	1		
	pN1	42	4.751	2.301-9.810	0.000
	pN2	50	7.015	3.514-14.008	0.000
Macroscopic lymph node metastasis	(-)	65	1		
	(+)	104	1.976	1.134-3.443	0.016
Adjuvant chemotherapy	(-)	77	1		
	(+)	92	1.123	0.686-1.841	0.644
Preoperative serum CEA	normal	136	1		
	high	33	2.281	1.330-3.911	0.003
Preoperative serum CA19-9	normal	134	1		
	high	35	2.068	1.207-3.542	0.008
Lateral lymph node dissection	(-)	26	1.983	1.111-3.539	0.021
	(+)	143	1		

TABLE 4 Multivariate Analysis of Prognostic Factors for Cumulative Survival

		Exp	C.I. 95%	*P* value
pT2		1		
pT3		2.386	0.884-6.439	0.086
pT4		6.547	2.080-20.607	0.001
pN0		1		
pN1		2.873	1.262-6.542	0.012
pN2		5.232	2.476-11.055	0.000
Lateral lymph node dissection	(+)	1		
	(-)	2.490	1.339-4.631	0.004

TABLE 5 Multivariate Analysis of Prognostic Factors for Disease-free Survival

		Exp	C.I. 95%	*P* value
pT2		1		
pT3		1.515	0.701-3.275	0.291
pT4		3.733	1.462-9.530	0.006
pN0		1		
pN1		4.877	2.343-10.150	0.000
pN2		5.852	2.834-12.083	0.000
Lateral lymph node dissection	(+)	1		
	(-)	2.074	1.154-3.726	0.015

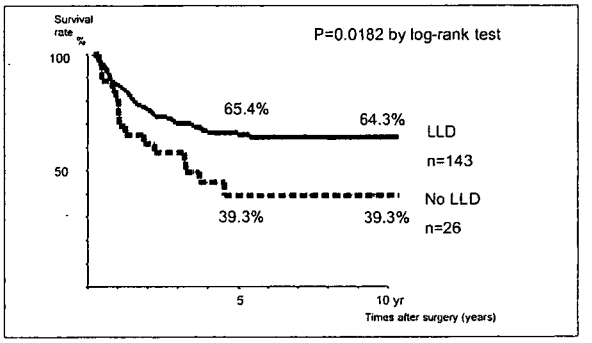

FIGURE 2 Disease-free survival curves of patients with and those without lateral lymph node dissection. LLD: lateral lymph node dissection. There were significant differences between the LLD group and No LLD group (p=0.0182 by log-rank test).