(25 mg/day) for 6 months (Group B; Fig. 1). When antitumor effects were observed with progressive disease (PD), the treatment was canceled and patients underwent surgery immediately. All patient data was collected by UMIN (UMIN000005668) and analyzed at the National Cancer Center in Japan. Tumors were measured by caliper before exemestane treatment began, and again in the eighth week of therapy. Tumor regression by clinical examination, pathological response, decisions regarding breast-conserving surgery, and safety assessments were the main outcome measures. All patients provided written informed consent. This investigational registration period was planned three years from May 2008. The trial was conducted in accordance with the principles of Good Clinical Practice as specified in the Declaration of Helsinki (Edinburgh, 2000). The study protocol was guided by the current regulations governing clinical trials, and was approved by the Ethics Committees of the individual hospitals involved. All patients gave written informed consent before study enrollment.

Study endpoints

The primary endpoints were objective response rates (ORR) by caliper at 4 and 6 months of treatment using an intention to treat analysis. Secondary endpoints were the rates of breast-conserving surgery or mastectomy, and the pathological response rates.

Clinical assessments

The primary study objective was to compare the differences between exemestane treatment for 4 and 6 months, using objective complete responses (CRs) and partial responses (PRs) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST),[9] which is based on caliper measurements of tumor size. Clinical response was assessed by comparing the longest diameter of the target lesions with the baseline measurement based on RECIST criteria. Every 4 weeks, patients underwent a physical examination, toxicity assessment, and tumor assessment using WHO criteria. If tumor progression was suspected, the tumor was further assessed by ultrasound or mammography. At baseline and immediately before surgery, the investigator recorded the extent of the least invasive feasible breast surgery option at that particular time: whether breast-conserving surgery or mastectomy was needed, or whether the tumor was inoperable.

Histological assessments

Histopathological therapeutic response was classified according to the General Rules for the Clinical and Pathological Recording of Breast Cancer 2005.[10] For Grade 0, no response was observed; Grade 1a comprised those tumors with mild changes in cancer cells regardless of the area, or marked changes seen in less than one-third of cancer cells; Grade 1b comprised tumors with marked changes seen in more than one-third but less than two-thirds of tumor cells; Grade 2 tumors contained marked changes in more than two-thirds of tumor cells; and Grade 3 tumors demonstrated a complete response, with no cancerous cells remaining. Mild changes included slight degenerative changes in cancer cells not suggestive of cell death (including cancer cells with vacuolation of the cytoplasm, eosinophilic cytoplasm, swelling of the nucleus, *etc.*). Marked changes include noticeable degenerative changes in cancer cells suggestive of cell death (including liquefaction, necrosis, and disappearance). The pathological response group was defined as tumors with Grade 1b and 2 responses. The non-response group was defined as tumors with Grade 0 and 1a responses.

Statistics

Based upon previous results, we assumed the response rate to be 40% and 60% after 4 and 6 months of exemestane, respectively (Table 1). To achieve an 80% statistical power, 46 examples were required to detect differences in both response rates with a 5% level of significance.[1] To account for attrition, we enrolled 50 patients.[11] Analysis was on an intention to treat (ITT) basis. The chi-squared test was used to compare tumor characteristics and responses, and rates of breast-conserving surgery between groups. Results with $p < 0.05$ were considered to be significant.

Results

Patient baseline characteristics

The study enrolled 52 post-menopausal women at 3 hospitals in Japan between April 25, 2008 and August 12, 2010. Of these, 26 patients were allocated to Group A, and 26 to Group B. One patient withdrew and did not complete the study (Group B). The main characteristics of the eligible patients are described in Table 2. The baseline characteristics were well balanced between the two treatment arms (Table 2).

Efficacy results

Evaluation of the primary efficacy endpoint (overall objective response as determined by clinical palpation) revealed that there was no statistically significant difference in the overall objective response (CR + PR) between the two treatment groups: Group A, 42.3%; Group B, 48.0%; $p = 0.89$ (Table 3). Clinically, 7.7% of Group A and 8.0% of Group B patients progressed while 50.0% and 44.0% of Group A and B patients, respectively, remained stable (not significant). As for the anti-tumor effect assessed by caliper at the eighth week, there were no differences between the two cohorts (Table 3). The pathological response rates of Groups A and B were 19.2% and 32.0%, respectively, a difference that was not statistically significant (Table 4, $p = 0.47$). Pathological CR in the primary breast lesion was only observed in one patient in Group B. Withdrawals from the trial due to side effects did not occur in either Group.

Table 2
Patients' baseline characteristics.

		Group A (4 months)	Group B (6 months)
Age, median (range)		66 (51–80)	64 (57–80)
Tumor stage, number (%)	T2	24 (92.3%)	24 (92.0%)
	T3	2 (7.7%)	2 (8.0%)
Nodal stage, number (%)	N0	21 (80.8%)	24 (92.0%)
	N1	5 (19.2%)	2 (8.0%)
Clinical stage, number (%)	IIA	19 (73.1%)	22 (84.0%)
	IIB	7 (26.9%)	4 (16.0%)
BMI[a]		23.9 (18.5–31.5)	24.5 (17.5–32.3)
Tumor diameter (caliper) Median (range) mm		30.5 (20–60)	30.0 (13–55)
Receptor status			
ER[b] positive/HER2[c] negative		25	22
ER[b] positive/HER2 positive		1	3
PgR[d]	Positive	20	18
	Negative	6	8

There were no differences between Groups A and B in these characteristics.
[a] BMI = body mass index.
[b] ER = estrogen receptor.
[c] HER2 = human epidermal growth factor receptor type 2.
[d] PgR = progesterone receptor.

Table 3
Clinical response (caliper).

Response[a]	Group A (4 months) number (26)		Group B (6 months) number (25)	
	8 weeks	16 weeks	8 weeks	24 weeks
CR	0	1	0	2
PR	7	10	5	10
SD	17	13	20	11
PD	2	2	0	2
Clinical ORR (CR or PR)	26.9%	42.3%	20.0%	48.0%

$p = 0.89$.
Complete Response: CR, Partial Response: PR, Stable Disease: SD, Progressive Disease: PD.
ORR: objective response rates.
[a] The RECIST methodology was used to assess response (Therasse et al., 2000).

Table 4
Clinical response (pathological response).

Pathological response[a]	Group A (4 months) number	Group B (6 months) number
3	0	1
2	0	1
1b	5	6
1a	15	13
0	6	4
Response rate (1b or 2 or 3)	19.2%	32.0%

$p = 0.47$.
0 no response, 1a mild response, 1b moderate response, 2 marked response, 3 complete response.
[a] Pathological response was defined as a Grade 1b, 2, or 3 lesion according to the following criteria.

Breast conservation

Of the 52 randomized patients, 32 would have required a mastectomy at baseline (17 in Group A and 15 in Group B; Table 5). For one of these patients, an operation was not performed. Surgery outcomes with respect to breast conservation improved in 4 of 26 patients in Group A (15.4%), as compared to 1 of 25 patients in Group B (4.0%). As compared to the intent-to-treat population, the increase in patients eligible for breast conserving surgery was numerically higher in Group A than Group B, although this difference did not reach statistical significance.

Discussion

ER-positive tumors are generally less sensitive to chemotherapy than ER-negative tumors.[12,13] Some trials have shown that tamoxifen is an effective primary endocrine agent for the treatment of locally advanced[14] and operable ER-positive breast cancers, especially in the elderly population.[15,16] A combined analysis of the IMPACT and PROACT clinical trials showed a trend toward better objective response rates when patients received aromatase inhibitors, but no statistically significant difference was observed between treatments with aromatase inhibitors or tamoxifen.[2,3] However, in the P024 trial, the objective response rate for treatment with aromatase inhibitors was significantly greater than that for tamoxifen.[4] At present, the optimum duration of treatment for neoadjuvant endocrine treatment is not known. Ideally, the timing would be based on individual patient response. Clinical trials report a common duration period of preoperative endocrine therapy as 4–6 months. Likewise, the duration of many neoadjuvant chemotherapy treatments is 6 months. Therefore, we carried out this study to compare the use of exemestane for 4 and 6 months prior to surgery. We found no significant differences in outcomes between patients who received the drug for 4 or 6 months; however, the latter group tended to have higher anti-tumor responses. It is thought that this observation did not reach statistical significance because we set the significant difference of both groups at 20%.Our study results show that the maximum response of neoadjuvant hormone therapy by exemestane is around four months. These data are consistent with the study by Antonio Llombart-Cussac et al.,[18] in which the maximum response to therapy with letrozole was at 4.2 months. In addition, a randomized phase II study[17] compared 4–8 months of letrozole in a single arm; there tended to have higher anti-tumor responses. We think that these results indicate that the maximum response to neoadjuvant hormone therapy is also around four months. ER- and/or PgR-positive tumors are biologically heterogeneous. It is thought that biologically heterogeneous groups require detailed statistical adjustment. Krainick-Strobel UE et al.[17] found that 4 months of neoadjuvant exemestane therapy improved the rate of breast-conserving surgery. There was not a large difference in response rates for treatments of 3–6 month duration; however, the anti-tumor effects tended to be greater after 6 months of treatment as compared to shorter time points. In our study, neither treatment group experienced severe side effects as a result of the therapy. However, Group B tended to have a higher pathological response rate. It seems that the maximum anti-tumor effect may be reached at different time points for each patient over the course of 24 weeks of treatment. Therefore, we cannot expect a large antitumor effect by treating for longer than 4 months; however, we could extend the treatment period until the time of operation. Furthermore, in addition to using exemestane as preoperative treatment in post-menopausal women with ER-positive breast cancer, due to the mild side effects observed during the 6 month course of treatment, we envision administering the drug over the long term under careful clinical supervision.

Table 5
Rate of breast-conserving surgery.

Group A (4 months)			Group B (6 months)		
	Estimation (pre treatment)	Post treatment		Estimation (pre treatment)	Post treatment
Mastectomy	17	13	Mastectomy	14	13
BCS[a]	9	13	BCS	11	12
Rate of BCS	34.6%	50%	Rate of BCS	44.0%	48.0%

[a] BCS = Breast-conserving surgery.

Ethical approval

The present work has been approved by the ethical committee of each institutional.

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Conflict of interest statement

All authors declare that they have no conflict of interest.

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特集／エビデンスに基づく乳癌診療の最前線

患者に優しい乳癌の新しい治療

ラジオ波焼灼治療の現状

井　本　滋

はじめに

ラジオ波焼灼治療（radiofrequency ablation, RFA）は肝細胞癌に対する標準治療の一つである。肝細胞癌の大半は肝炎ウィルスに起因する固形癌であることから切除後の再発率は50%以上と高い。従ってRFAは侵襲を伴う開腹手術に比べて負担が少なく，繰り返し治療できる点が優れている。現在，腎癌，肺癌，甲状腺癌，悪性腫瘍の骨転移などさまざまな領域でRFAの有効性について検証が進められている。では，乳癌におけるRFAはどのような位置付けにあるのか？　残念ながら，現時点でのエビデンスレベルはレベル4ないし5相当である。本稿では乳癌治療におけるRFAの現状と臨床試験について述べる。

Ⅰ．乳癌の特性と集学的治療におけるRFA

乳癌は乳管癌と小葉癌に大別されるが，小葉癌は比較的広範囲に広がる傾向がある。乳管癌も浸潤・非浸潤を問わず乳管内に進展することが多い。Hollandらは浸潤性乳管癌の乳房切除標本の連続切片を作成し，乳管内進展（extensive intraductal components, EIC）のある群とない群を対象に，浸潤性乳管癌の辺縁からどこまで乳管内癌（intraductal carcinoma）が存在するか検討した（図1）[1]。その結果，辺縁から2cmの距離においてEICあり群では33%の症例で乳管内癌が存在したのに対しEICなし群では2%のみであった。臨床試験のメタアナリシスでは，n0乳癌における乳房部分切除では乳房照射の有無によって10年乳房内再発率は19%の差があった[2]。乳癌は腫瘍周囲乳管内癌の広がりを認めることが多いため乳房照射を伴う乳房部分切除が標準治療である。一方，RFAは乳房部分切除の代替治療であるから，乳房部分切除と同等の予後が期待されなければならない。

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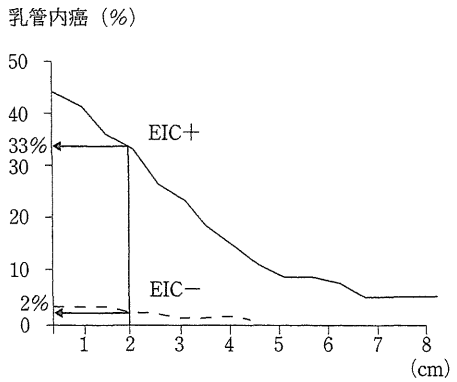
Ⅱ．乳癌におけるRFAの基礎

1．適　応

まずRFAによる焼灼範囲の側面から検討すると，MRIによるEICの治療前評価は必須である。腫瘍径が小さくてもEICが認められる場合は焼灼範囲を超えて癌が遺残する。マンモグラム上で観察される乳癌に伴う広範な石灰病変を伴う症例はRFAの適応外である。乳腺は容量の大きい肝臓と異なり皮膚あるいは大胸筋に囲まれており，周囲臓器への熱傷を防ぐには自ずと焼灼範囲が限定される。以上から，乳癌のRFAは，EICを含めて2cm以下の腫瘍径で，乳頭乳輪の近傍になく皮膚に引きつれを認めず大胸筋膜に接しない腫瘍が適応である[3]。

次に腫瘍の性状に伴う集学的治療の側面から検討すると，RFA前の組織生検は必須である。その結果，Ki67高値やHER2陽性など増殖能の



（Holland, R., J Clin Oncol, 8: 113-118, 1990.より改変）

図1　乳管内進展（EIC）の有無と腫瘍縁からの乳管内癌の存在

表 1　切除を伴うRFA

著者（報告年）	症例数	T	電極針	焼灼率	合併症（症例数）
Jeffrey (1999)	5	T2-3	LeVeen	80%	None
Izzo (2001)	26	T1-2	LeVeen	96%	Skin burn (1)
Burak (2002)	10	T1	LeVeen	90%	None
Singletary (2003)	29	T1-2	RITA	86%	Skin burn (1)
Hayashi (2003)	22	T1	RITA	64%	Skin burn (1)
Noguchi (2006)	10	T1	RITA	100%	None
Khatri (2007)	15	T1	Cool-tip	93%	Skin puckering (2) Wound infection (1)
Medina-Franco (2008)	25	T1-2	Elektrotom	76%	Skin burn (3) Wound infection (1)
Imoto (2009)	30	T1	LeVeen	87%	Skin burn (2) Muscle burn (7)
Hung (2009)	20	T1	LeVeen or Cool-Tip	90%	None
Kinoshita (2010)	49	T1-2	Cool-tip	61%	Skin burn (2) Muscle burn (3)
Ohtani (2011)	41	T1	Cool-tip	88%	Skin burn (1)
Total	282	T1-3	Various	83%	Skin burn (11) Miscellaneous (18)
		T1		86% (152/177)	

高い乳癌では化学療法が初期治療である。腫瘍径の大きな乳癌でも薬物療法によって腫瘍が縮小しRFAが可能となる場合も想定されるが，焼灼することで生物学的特徴に関する情報が失われてしまうことは医学的にも倫理的にも許容されない。以上から，手術先行となる悪性度の低い乳癌，例えばルミナルA相当がRFAの適応である。但し，乳管癌，小葉癌，特殊型など組織型に関する適応の是非は課題である。

2. 基本手技

乳癌RFAではCool-tip型とLeVeen型のRF generatorを用いた報告が多く見られる。電極針は腫瘍中心を貫通するようにエコーガイド下に挿入する。腫瘍径に応じて電極針のサイズを調整し適切な焼灼範囲を確保する。皮膚または大胸筋に近接する場合は，エコーガイド下に皮下あるいは大胸筋膜上に5％ブドウ糖水を注入し焼灼に伴う皮膚熱傷や胸筋熱傷を予防する。RF generatorによる電力の初期設定は10Wから開始し，毎分5～10Wずつ上昇させる。電力上昇に伴いジュール熱が発生し，腫瘍並びに腫瘍周囲組織が焼灼される。完全に焼灼されると，電極針で計測される電気抵抗（impedance）は最大値（Ω）となり急速に電圧が低下するため焼灼終了の目安となる（ロールオフ現象）。焼灼時間は数分から数十分である。焼灼中および焼灼終了後数時間は，氷あるいは保冷剤によって患側乳房の冷却を行う。

3. 熱変性による病理組織診断

RFAによる焼灼温度は70度を超えるため，焼灼領域の細胞は熱変性する。焼灼直後に切除された細胞は，HE染色によって核の膨張や濃染像が認められる。しかし，組織構築自体の変化に乏しく細胞の生死の判断は困難である。熱変性した細胞は時間経過とともに融解しマクロファージに貪食されるが，その時期は不明確であり客観的にcell viabilityを評価する必要がある。Nicotinamide adenine dinucleotide（NADH）diaphorase染色はミトコンドリアに局在し，NADとNADHの2つの状態をとり酸化還元反応に必須の補酵素であり，熱変性による細胞死の評価に適している[3]。生細胞であればミトコンドリアが赤紫色に染色されるが，死細胞では染色されない。抗サイトケラチン抗体や抗ssDNA抗体によるcell viabilityの評価も試みられている[4]。

Ⅲ. 乳癌におけるRFAの治療成績

1. 乳房切除を伴うRFA

RFAによってEICを含めた腫瘍部が完全に焼灼されているかどうか検討することは重要である。表1はRFAを施行した直後あるいは数週間後に乳房切除術を施行した報告である。

表 2　切除を伴わない RFA

著者（報告年）	症例数	T	電極針	観察期間（月）	再発（症例数）
Susini (2006)	3	T1	Cool-tip	18 (mean)	None
Marcy (2007)	5	T1-2	Elektrotom	24～36	IBTR* (1)
Oura (2007)	52	Tis-1	Cool-tip	6～30	None
Nagashima (2009)	17	T1	Cool-tip	12～28	None
Yamamoto (2011)	30	T1	Cool-tip	2～41	None
Yoshinaga (2013)	8	T1	Cool-tip	38 (mean)	None
Noguchi (2013)	19	T1	RITA	37～82	Liver (1)
Imoto (2013)	20	T1	LeVeen	3～45	None
Total	154			2～82	(2)

(*IBTR, ipsilateral breast tumor recurrence)

どれも小規模な研究である。対象の腫瘍径や電極針もさまざまである。さらに，HE 染色，NADH diaphorase 染色など完全焼灼の判定もさまざまである。282例の検討では焼灼率が64%から100%であり，主な合併症は皮膚熱傷（4%）であった。仮に T1 乳癌を対象とした報告のみを集計すると，焼灼率は177例中152例の86%であった。

2. 乳房切除を伴わない RFA

RFA は究極の非切除による乳癌治療である。よって，切除を行わずに RFA のみで経過観察を試みた報告も存在する（表 2）。表 1 と大きく異なる点は，対象の腫瘍径である。ほとんどが T1 以下の症例であり RFA の適応基準に合致している。その結果，154例について観察期間は 2 ヵ月から82ヵ月と幅があるものの，乳房内再発はわずか 1 例（0.6%）であった。筆者らは20例の検討を行った。その中で，MRI による RFA 後の経過観察が有用であることを報告した[5]。切除を伴う RFA の経験から，MRI によるほぼ無信号な焼灼範囲は RFA 後の組織で認められたうっ血した境界（red ring formation）と一致していることが示唆された（図 2）。乳癌低侵襲治療研究会では切除を伴わない乳癌 RFA の症例について後向き解析を行った[6]。その結果，10施設から497例が集計された。平均腫瘍径は1.6cmで T1 乳癌が425例（86%）であった。RFA 後の観察期間の中央値は50ヵ月であったが，T1 乳癌と T2 以上乳癌の 5 年乳房内非再発率は96%と80%であった。以上から，EIC を伴わない T1 乳癌であれば，RFA が乳房部分切除の代替治療として容認される可能性は高い。

Ⅳ. 乳癌非切除治療に関する臨床試験

筆者らは Cool-tip 型の電極針と RF generator を用いて，切除を伴わない乳癌 RFA の多施設共同第Ⅱ相試験を行っている（図 3）。対象は EIC を含めて 2 cm以下の 0 期または ⅠA 期乳癌である。Primary endpoint は病理学的な完全焼灼率である。RFA 後 4 週目に組織生検を行い，完全焼灼の有無について中央判定を行う。病理学的にも画像診断上も癌の遺残がなければ乳房照射と悪性度に応じた薬物療法を施行し10年間の経過観察を行う。試験は 2 step design で検定され，最初の 9 例が登録された時点で中間解析を行い，試験の継続の有無を決定する。最終的な目標症例数は32例である。

米国では American College of Surgeons Oncology Group（ACOSOG）Z1072 試験が実施された。これは切除を伴う乳癌の凍結治療（cryoablation）に関する第Ⅱ相試験で primary endpoint は RFA 同様に complete tumor ablation である。99例の登録は本年 5 月で終了し，現在解析作業とのことである（主研究者である Duke 臨床研究所の David. M. Ota 教授より私信にて）。

ま　と　め

乳癌における RFA あるいは cryoablation はその対象が限定される。以前，筆者が MD アンダーソンがんセンターを訪問した際に，乳腺外科の准教授から小さな腫瘍に RFA をしなくても小さな傷で切除できるのであるから馬鹿馬鹿しいと言われた。確かにその通りである。しかし，RFA はエコーガイド下の組織生検に馴れ

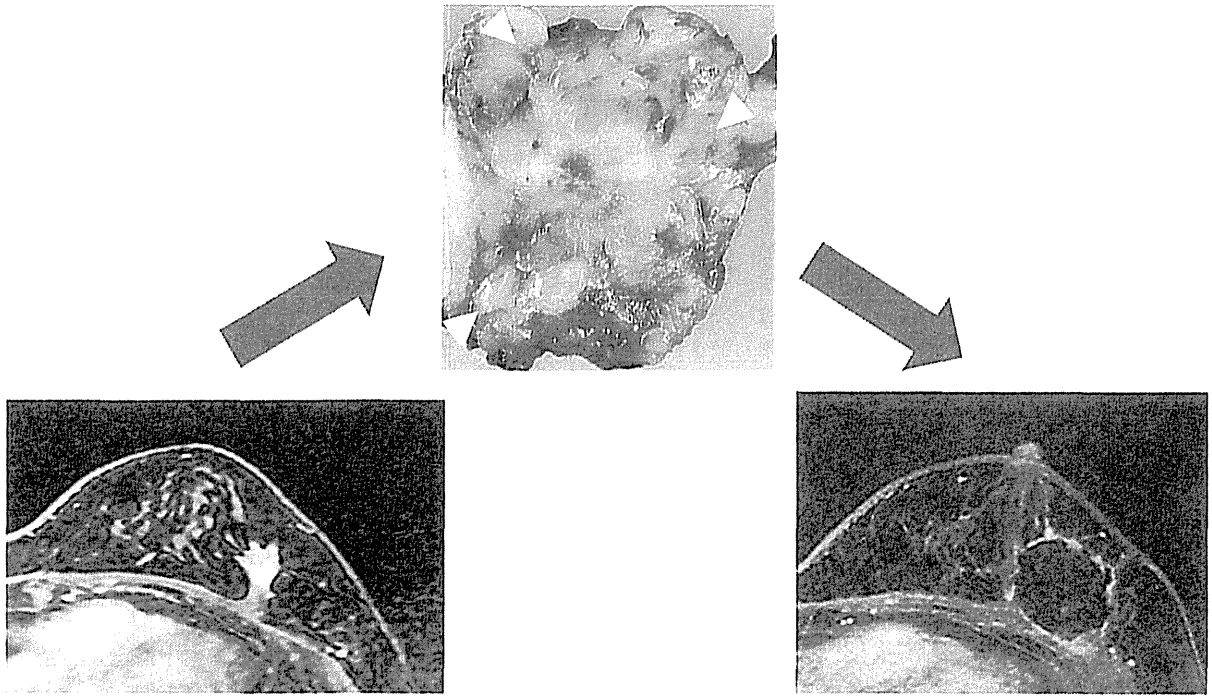


図　2　焼灼による red ring formation（矢尻）と MRI 上の焼灼領域との関係

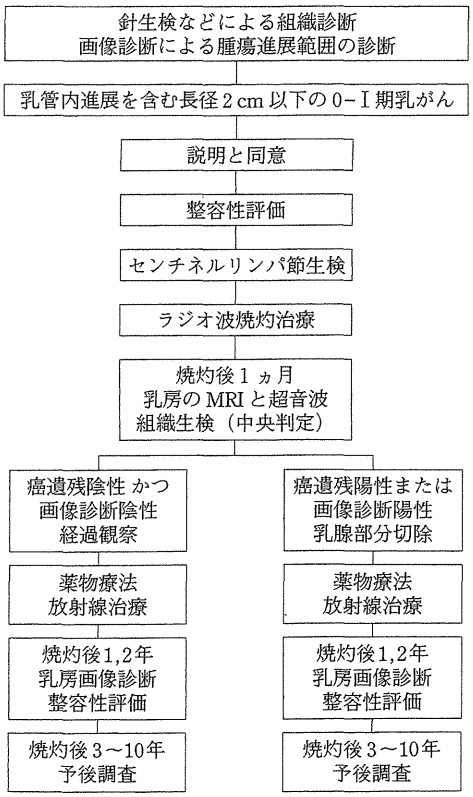


図　3　広範な乳管内進展を伴わない 0-Ⅰ期乳がんに対するラジオ波焼灼治療の安全性と有効性に関する第Ⅱ相臨床試験

た外科医あるいは画像診断医であれば，乳房にメスを入れずに行うことができる究極の低侵襲治療である。彼の批判に答えるには，第Ⅲ相試験が必要である。残念ながら，乳房部分切除と比較する第Ⅲ相試験は非現実的である。理由は，対象が全乳癌の数%でかつ予後良好な症例を選別することになるからである。対象は EIC が限局していることから乳房温存療法を施行した場合の乳房内再発率は極めて低いことが予想される。以上から，endpoint の設定にも寄るが，RFA と乳房部分切除の治療効果に関する非劣性を検証する場合，少なくとも千例以上の症例登録が見込まれる。もし千例を 4 年で集積し，かつ適格条件を満たす症例が全乳癌の 5 %と仮定すると，年間 5 千例の乳癌手術を行う施設数が必要である。しかし，同意取得率が半数ならば 1 万例の乳癌手術を行う施設数を要する。そして 5 年以上の経過観察である。では，RFA は乳癌治療としての将来を諦めるべきか？　ACOSOG が cryoablation の試験を行っているように非切除治療への関心は世界的に高まりつつある。現在，国立がん研究センター中央病院が中心となり先進医療における乳癌 RFA の試験が計画されている。少なくともレベル 3 のエビデンスに相当する前向き研究は必須であるが，将来的には RFA が保険診療として，あるいは医療の国際化と規制緩和の潮流を受けて混合診療として行われる日が来ることを期待する。

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CASE REPORT

Rectoseminal vesicle fistula as a rare complication after low anterior resection: a report of three cases

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Abstract A rectoseminal vesicle fistula is a rare complication after a low anterior resection for rectal cancer, usually developing in the outpatient postoperative period with pneumaturia, fever, scrotal swelling or testicular pain. A diagnostic water-soluble contrast enema, cystography and computed tomography reveal a tract from the rectum to the seminal vesicle. Anastomotic leakage is thought to be partially responsible for the formation of such tracts. This report presents three cases of rectoseminal vesicle fistula, and the presumed course of the disease and optimal treatment options are discussed.

Keywords Colon fistula · Seminal vesicle · Urinary fistula

Introduction

The complications of end-to-end anastomosis for lower rectal cancer include anastomotic leakage, rectovaginal fistula, intrapelvic abscess and stenosis. A rectoseminal vesicle fistula is rare. Three patients developed rectoseminal vesicle fistula and were treated over a period of 19 years. This report reviews and summarizes similar previously reported cases, while focusing on the presumed course of the disease, diagnostic procedures and treatment options.

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Patient 1

A 73-year-old male was admitted to the surgical department for treatment of rectal cancer 7 cm from the anal verge. Colonoscopy revealed a type 2 tumor of the rectum and the histopathological examination of a specimen obtained by colonoscopy revealed adenocarcinoma. Laboratory tests were normal. The preoperative staging was T3N0M0. The patient did not receive any neoadjuvant therapy.

A low anterior resection was performed with an end-to-end anastomosis. Microscopic examination of the specimen revealed well-differentiated adenocarcinoma of the rectum with adequate resection margins and no metastases in the 12 resected lymph nodes. This was a T3N0M0 tumor, according to World Health Organization (WHO) classification.

The immediate postoperative course was uneventful. The discharge from the intrapelvic drain was noted to be purulent on postoperative day 7. A water-soluble contrast enema demonstrated minor anastomotic leakage on day 14. The patient was treated conservatively with intrapelvic drainage and antibiotics. Oral diet was resumed on postoperative day 24 and the patient was discharged on day 29. He was readmitted on postoperative day 37 with acute left testicular pain, fever and pneumaturia. A vasogram followed by fistulography demonstrated a fistula from the seminal vesicle to the rectum via the anastomotic site (Fig. 1).

Computed tomography revealed air bubbles located between the rectum and seminal vesicle. Anastomotic leakage followed by coloseminal vesicle fistula after low anterior resection was diagnosed. The leakage was locally restricted, without any sign of generalized peritonitis, and was successfully treated using only urethral catheterization

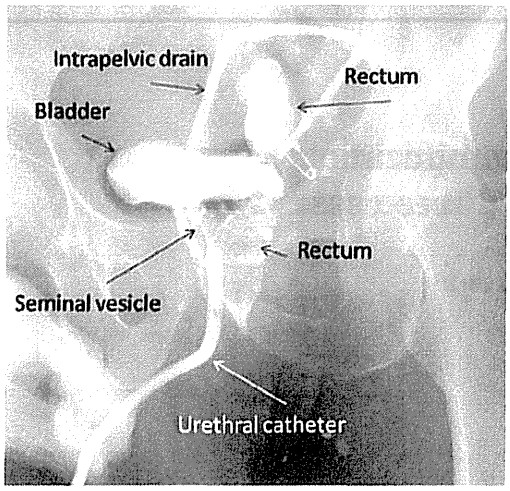

Fig. 1 A vasogram followed by fistelography demonstrating fistula from the seminal vesicle to the rectum via the anastomotic site. 136 × 128 mm (150 × 150 DPI)

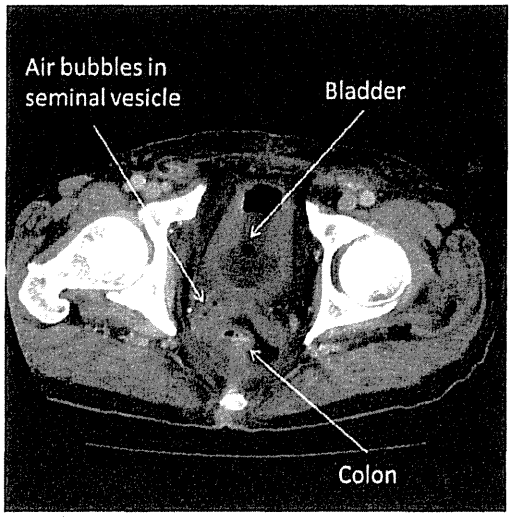

Fig. 2 CT showing air bubbles in and around the seminal vesicle. This slice is 1 cm above the anastomotic site. 125 × 125 mm (150 × 150 DPI)

and antibiotics with oral diet. The fistula had successfully healed by postoperative day 62, or 25 days after readmission.

Distant metastases were found 17 months after the first operation. The patient underwent partial hepatectomy and pulmonary resection for metastases from rectal cancer. He is doing well without local recurrence at 4 years after the first operation.

Patient 2

A 76-year-old male was admitted to the surgical department for treatment of rectal cancer 7 cm from the anal verge. Colonoscopy revealed a type 2 tumor of the rectum and the histopathological examination of a colonoscopic specimen led to a diagnosis of adenocarcinoma. Laboratory tests yielded normal results. The preoperative stage was T3N1M0. The patient's medical history included diabetes mellitus, hypertension, angina pectoris and pulmonary hypertension. The patient did not receive any neoadjuvant therapy.

A low anterior resection was performed with end-to-end anastomosis. A microscopic examination of the specimen revealed moderately differentiated adenocarcinoma of the rectum with adequate resection margins and lymph node metastasis in one of the 12 resected nodes. This was a T3N1M0 tumor.

The patient accidentally removed the urethral catheter while the balloon was still inflated on postoperative day 7. No apparent damage was observed in the urethra at that time. He was discharged on postoperative day 11. He presented to the emergency department 1 month after first discharge with acute testicular pain, pneumaturia and a swollen scrotum. A water-soluble contrast enema demonstrated a fistula between the anastomotic site and a seminal vesicle. CT revealed air bubbles around the seminal vesicle and a series of abscesses from the seminal vesicle to the scrotum (Fig. 2). Conservative therapy with antibiotics and urethral catheterization was attempted which failed, so diverting transverse colostomy was performed on postoperative day 50 (day 39 after readmission). Healing of the fistula was confirmed at another hospital and stoma closure was eventually performed, about 14 months after the first operation.

The patient was treated for pulmonary metastases with oral tegafur-uracil. He has survived 3 years and 10 months since the first operation without local recurrence.

Patient 3

A 49-year-old male was admitted to the surgical department for treatment of a huge rectal cancer. Colonoscopy revealed a type 3 tumor of the rectum and a histopathological examination led to a diagnosis of adenocarcinoma. Computed tomography (CT) and magnetic resonance imaging demonstrated the tumor and adjacent abscess forming a mass 10 cm in diameter, with infiltration into the right seminal vesicle. The C-reactive protein level was elevated to 7.1 mg/dl. Pelvic incisional drainage was performed prior to the radical operation. Preoperative staging was T4N2M0.

A low anterior resection of the tumor with the bilateral seminal vesicles and diverting ileostomy were performed with end-to-end anastomosis. A microscopic examination of the specimen revealed moderately differentiated

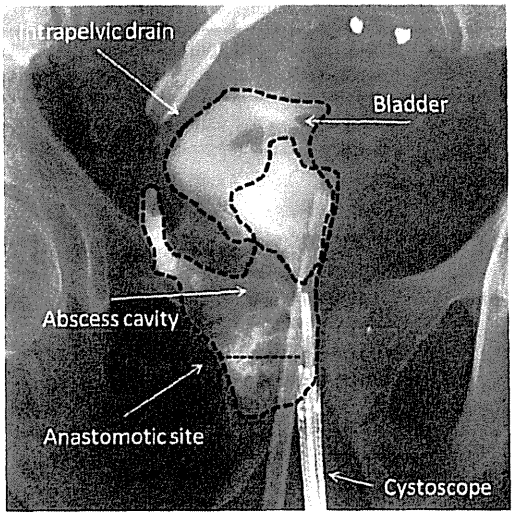

Fig. 3 A vasogram under cystoscope control demonstrates fistula from the ejaculatory duct to the anastomotic site via an abscess cavity. 137 × 137 mm (150 × 150 DPI)

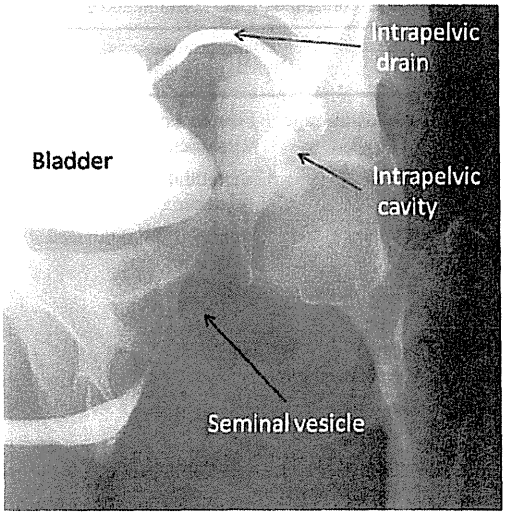

Fig. 4 Retrograde cystourethrography shows fistulous communication between the seminal vesicle and intrapelvic cavity. This represents seminal vesicle fistula after concomitant resection of rectum and seminal vesicle. 125 × 125 mm (150 × 150 DPI)

adenocarcinoma of the rectum with adequate resection margins and no metastases in any of the 44 resected lymph nodes. This was a T3N0M0 tumor.

The patient displayed fever and fecaluria on postoperative day 10. CT revealed anastomotic leakage surrounded by a cavity filled with pus and an increased air–water level. A vasogram under cystoscopic control demonstrated a fistula from the ejaculatory duct to the anastomotic site via an abscess cavity (Fig. 3). He was diagnosed with anastomotic leakage followed by creation of a fistula between the anastomotic site and the excision site of the seminal vesicles. The patient was effectively treated using lavage from an intrapelvic drainage tube and urethral catheterization with a saline flush. The abscess cavity gradually contracted and disappeared, but the fistula remained refractory. Gracilis muscle flap closure was attempted but proved unsuccessful. Additional abdominal rectus muscle flap closure achieved an improvement of the fistula.

The patient finally underwent total pelvic exenteration for intrapelvic recurrence along with intention to treat urinary division after 2 years and 6 months. He has survived 3 years since the first operation.

Discussion

Abscess formation around the seminal vesicle is infrequently encountered in patients without apparent anastomotic leakage that have undergone concomitant resection of the rectum and seminal vesicle (Fig. 4). The usual clinical course is cloudy discharge from the pelvic drain, fever, and relatively normal results of laboratory tests, other organ function and general status. A water enema of the anastomotic site subsequently reveals no leakage. Cutting off the root of the seminal vesicle without ligation causes a seminal vesicle fistula and local collection of pus. Simply leaving the fistula open may be adequate as long as the fever is controlled by antibiotics. The patient usually recovers from the fistula within several weeks. The prophylactic approach includes a ligation of the base of the resected seminal vesicle.

This report presented three cases of rectoseminal vesicle fistula after low anterior resection. Low anterior resection has been performed at this institution since 1992, with more than 1100 patients treated. Three patients developed rectoseminal vesicle fistula and were treated over a 19 years period. Coloseminal vesicle fistula is particularly uncommon. The causes or origin of such fistulae include inflammatory bowel disease, low anterior resection, prostatectomy, radiation proctitis, and sigmoid colon diverticula [1–3]. Only 10 cases of seminal vesicle fistula were found among the reported postsurgical intervention cases [3–9] (Table 1).

Minor leakage was demonstrated on postoperative day 14 in the first case, and was conservatively treated using only a drainage tube. Mild residual inflammation might have adversely influenced the fragile seminal vesicle wall. Outpatient follow-up on postoperative day 37 revealed a fistula to the seminal vesicle. Denonvilliers' fascia, which is located between the rectal anterior wall and the seminal vesicle beneath the level of the peritoneal reflection, may be removed when performing total mesorectum excision [10]. Denonvilliers' fascia is a very strong tissue that divides the urinary tract and rectum. Infectious material

Table 1 Clinical features, diagnostic examinations, and treatment of patients with postoperative coloseminal vesicle fistula

Author	Cause	Symptoms	Urine passage	Onset	Diagnostic examination	Initial treatment	Radical treatment
Goldman [4]	LAR leakage	Pneumaturia, bacteriuria testicular pain,	No	1 month	Water-soluble contrast enema	Cutaneous vasotomy	None
Kollmogen [5]	APR	Urethral discharge, fever, dysuria	No	10 days	Sinography	Antibiotics, drainage	None
Carlin [6]	Crohn's	Discharge from perineal sinus	No	15 years	CT sinography	N.S.	None
	AR	None	No	2 months	CT with rectal contrast enema	Drainage	APR
Calder [7]	Open prostatectomy	N.S.	N.S.	N.S.	Water-soluble contrast enema	N.S.	N.S.
Celebrezze [8]	Prostatic brachytherapy	Rectal ulcer	Yes	2 years	N.S.	Mucosal flap	Diversion
	Prostatic brachytherapy	Rectal bleeding	Yes	15 months	N.S.	Mucosal flap	Colostomy
Kawasaki [9]	LAR leakage	Dysuria	No	2 weeks	Water-soluble contrast enema	Conservative	Colostomy
Our cases	LAR leakage	Pneumaturia, testicular pain, fever	No	1 month	CT and vesiculography	Urinary catheter	None
	AR	Pneumaturia, testicular pain, scrotal swelling	No	2 weeks	CT and contrast enema	Urinary catheter, antibiotics	Colostomy
	LAR leakage	Fecaluria, fever, scrotal swelling	Yes	1 week	CT and vasogram	Urinary catheter, antibiotics	Muscle flap

LAR low anterior resection, *AR* anterior resection, *APR* abdominoperineal resection, *N.S.* not stated

may cause local tissue destruction and the formation of a fistula if this septum is resected.

The second case showed no evidence of anastomotic leakage during the postoperative course. Latent anastomotic leakage may have been present or the fragile seminal vesicle wall may have eventually collapsed, allowing passage between the seminal vesicle and anastomotic site in the outpatient follow-up period. Accidental catheter removal may have adversely affected the urinary tract, with injury of the ejaculatory duct and seminal vesicle causing fistula to the rectum. However, a seminal vesicle fistula is rarely observed in cases with accidental removal of a urethral catheter.

The third case required resection of a huge T4 mass, including the bilateral seminal vesicles. A Retzius cavity approach was selected due to the size of the tumor occupying the pelvic cavity, and the bases of the seminal vesicles were difficult to identify for ligation. Anastomotic leakage caused the abscess formed by leakage to increase in size around the remnant rectum, and become a seed of inflammation, leading to a fistula into the unclosed ejaculatory duct.

Rectoseminal vesicle fistula formation in all three cases appeared to be due to a combination of resection of Denonvilliers' fascia or the seminal vesicle itself and anastomotic leakage.

Many investigators have evaluated the safety of the double stapled technique and its role in rectal cancer surgery. They concluded that the double stapling technique is an equivalent or even superior type of intervention with respect to speed, sterility and anastomosis safety, while also associate with fewer complications [11–20]. However, Kosugi et al. [21] reported that the incidence of rectovaginal fistula was higher in patients who were anastomosed by the double stapled technique or had concomitant resection of the vaginal wall. The current surgical reports and postoperative examinations proved no direct relationship between the double stapled technique and fistulae. However, these reports concerning rectovaginal fistula [21–23] emphasize that the double stapled technique might cause rectoseminal vesicle fistula when frustrating distal anastomosis is carelessly performed.

No diverting stoma was constructed in the first two cases. The first case recovered conservatively, but the other was treated with transverse colostomy. The third case required the construction of a diverting ileostomy, but it failed. These cases suggest that a diverting stoma cannot always prevent leakage or the formation of rectoseminal vesicle fistula. Several studies have shown the absence of a diverting stoma to be a risk factor for leakage after LAR [24–29], whereas others did not [30]. Anastomotic failure and the completion of rectoseminal vesicle fistula are thought to be influenced by an infectious environment, the viscosity of the discharge and the rectum-cavity urinary tract pressure gradient. Whether diverting the fecal stream

in itself directly prevents fistula formation between the urinary tract and fragile rectal wall remains to be proven.

The symptoms of fever, pneumaturia, scrotal swelling and testicular pain were seen in these three cases (Table 1). Some late-onset cases are described in the literature, as in the present cases. A fistula therefore needs to be considered in patients who show fever, pneumaturia, scrotal swelling or testicular pain, particularly in cases with evidence of anastomotic leakage in the postoperative period.

These three cases indicate that conservative therapy may be an option when the patients develop a rectourethral fistula arising from minor leakage. Antibiotics, urinary catheterization, and percutaneous drainage are effective in well-chosen cases. Although unsuccessful in the third patient, gracilis muscle or abdominal rectus muscle flap closure may be viable treatment options when a diverting stoma had been established in the first operation [31]. The radical diversion of either or both the urinary and fecal streams may be applicable in cases with apparent urine passage and extended infection.

Conclusions

Pneumaturia, fever, scrotal swelling and testicular pain are signs of a rectoseminal vesicle fistula in patients following anterior resection for rectal cancer. The resection of Denonvilliers' fascia and anastomotic leakage appear to represent risk factors for this complication. These symptoms may emerge within a few days or several weeks into the postoperative period. A water-soluble contrast enema and CT are effective diagnostic examinations which may lead to appropriate therapeutic options. Local medical or surgical therapy will do well in some cases. Unsuccessful fistulae should be treated with urinary or fecal diversion, or both. Selection criteria for conservative therapy include the severity of the anastomotic leakage, extent of abscess formation and passage of urine through the fistula.

Conflict of interest None of the authors have any conflicts of interest to disclose.

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ORIGINAL CONTRIBUTION

Clinical Impact of Elastic Laminal Invasion in Colon Cancer: Elastic Laminal Invasion-Positive Stage II Colon Cancer Is a High-Risk Equivalent to Stage III

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BACKGROUND: Elastic laminal invasion is defined as tumor invasion beyond the peritoneal elastic lamina. It is one of the factors affecting the prognosis of patients with colon cancer.

OBJECTIVE: This study aimed to investigate the clinical impact of elastic laminal invasion in colon cancer and the magnitude of the worse prognosis of elastic laminal invasion-positive, node-negative patients.

DESIGN: This was a retrospective cohort study.

SETTINGS: This study reviewed data from a tertiary care cancer center in Japan.

PATIENTS: The records of 436 patients with pT3 or pT4a colon cancer who underwent curative resection between January 1996 and December 2006 were reviewed.

MAIN OUTCOME MEASURES: The primary outcome measure was recurrence-free survival. Cox regression analyses established the factors associated with recurrence-free survival. Six groups formed by combining the factors were compared.

RESULTS: Of the patients with pT3 disease, those who were positive for elastic laminal invasion had a 5-year recurrence-free survival rate of 73.8% compared with a rate of 85.0% in those who were negative for elastic laminal invasion and 53.5% in patients with pT4 disease. Three unfavorable prognostic factors were identified, including lymph node metastasis, positive elastic laminal invasion, and a lack of adjuvant chemotherapy. Log-rank analysis revealed statistically significant differences in recurrence-free survival between group 1 (node negative, elastic laminal invasion negative, and no adjuvant chemotherapy) and group 3 (node negative, elastic laminal invasion positive, and no adjuvant chemotherapy). The HR for group 1 compared with group 3 was 0.49 (95% CI, 0.27–0.90). Furthermore, the HRs for group 2 (node positive, elastic laminal invasion negative, and received adjuvant chemotherapy) and group 4 (node positive, elastic laminal invasion positive, and received adjuvant chemotherapy) vs group 3 were 0.77 (95% CI, 0.35–1.69) and 1.36 (95% CI, 0.62–2.98).

LIMITATIONS: Our study has limited prediction accuracy of our prognostic stratification, and an analysis of small subgroups may not have been capable of detecting significant differences. In addition, a wide range of hematoxylin and eosin- and elastica-stained slides were examined per case.

CONCLUSIONS: Elastic laminal invasion adversely influences prognosis in pT3 and pT4a colon cancer. Although elastic laminal invasion positivity does not affect prognosis in node-positive patients receiving adjuvant chemotherapy, node-negative patients with elastic laminal invasion have a similar risk of recurrence as node-positive patients.

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KEY WORDS: Colon cancer; Elastic laminal invasion; High-risk stage II; Serosal invasion.

In 2008, 1.2 million people received a new diagnosis of colorectal carcinoma (CRC), and 608,700 patients died of the disease, making it the fourth most common cause of cancer death globally.[1] However, in the United States and Europe, it is the second leading cause of cancer death.[2,3] In Japan, CRC is diagnosed in ≈105,000 patients each year and accounts for 42,000 deaths, making it the third leading cause of death from cancer.[4]

CRC is staged using the TNM system of the International Union Against Cancer (UICC),[5] in which primary tumor extension (T), regional lymph node involvement (N), and the presence of distant metastasis (M) are established to guide treatment and predict prognosis. Pathologic (p) T categories are divided into pT1 to pT4: pT3 disease is defined by subserosal tumor invasion and accounts for approximately half of all cases of CRC. The prognosis of patients with pT3 disease varies, which may be explained by differences in the depth of tumor invasion.[6–8] Nevertheless, although it has been suggested that pT3 disease be subclassified, it currently remains 1 category.

The peritoneal elastic lamina (PEL) is a component of the normal intestinal wall and can be identified histologically by elastica staining. It is situated beneath the visceral peritoneum and invests the intestinal wall. Subclassifying pT3 tumors according to their relationship with the PEL has been suggested as another method of pT3 classification. Patients with tumor invasion beyond the PEL are classified as having elastic laminal invasion (ELI).[9] Furthermore, the elastic lamina is used as a landmark of invasion of the visceral pleura in the TNM classification of lung cancer.[5] These facts guide us to focus on the PEL as a landmark of the classification of tumor spread.

Our previous study of 564 patients with stage II to IV CRC suggested that ELI was one of the factors affecting the prognosis of patients with colon cancer (CC) and an independent risk factor for tumor recurrence only among CC patients with stage II disease.[10] However, it is not yet clear that ELI status can be a prognostic factor under comprehensive analysis, including factors such as lymph node involvement and adjuvant chemotherapy.

The aim of this study was to investigate the clinical impact of ELI in patients diagnosed with pT3 and pT4a CC and the magnitude of the worse prognosis of patients with ELI-positive, node-negative CC (NNCC).

MATERIALS AND METHODS

Patients Selection and Follow-up

Of the 1103 consecutive patients who underwent surgery for CC at the National Cancer Center Hospital East between January 1996 and December 2006, 721 patients had pT3 or pT4a disease. The following patients were excluded: 1) patients with multiple or metachronous CC, 2) patients simultaneously or previously diagnosed with an advanced tumor other than CC, 3) patients with distant metastasis, 4) patients who received neoadjuvant therapy, and 5) patients in whom resection was incomplete (R1 and R2). Completeness of resection was classified as R0 (negative gross and pathologic margins), R1 (negative gross and positive microscopic margins), and R2 (positive gross margins). R1 and R2 were defined as incomplete resection. After exclusions, the clinical records of 439 patients with pT3 and pT4a CC were retrospectively studied. We began routinely administering 5-fluorouracil–containing adjuvant chemotherapy for patients with stage III disease in 2003, and 3 patients with stage II CC were excluded because they had also received adjuvant chemotherapy. Each patient's prospectively collected demographic, staging, histopathology, and prognostic outcome data were recorded. All of the cases were reclassified based on the 7th edition of the UICC TNM staging system.[5] We did not categorize isolated tumor deposits as pN1c to avoid overestimating the prognosis of patients with stage III disease. Follow-up after surgery was composed of serum tumor marker measurement every 3 months and chest and abdominal CT every 6 months for the first 3 years, then every 6 months for the next 2 years, and annually for 2 additional years. All of the patients were followed from the date of surgery to the last contact (death or last follow-up) or until December 31, 2011. Recurrence was defined as distant metastasis, local recurrence, or peritoneal dissemination; the final diagnosis was made by imaging (CT, MRI, and/or positron emission tomography CT), cytologic analysis, or biopsy, if necessary.

Written, informed consent to tissue collection and use for research was obtained. Conduct of the study was approved by our local ethics committee (National Cancer Center Hospital, No. 2012-067).

Histopathologic Analysis

We used the same histopathologic protocol as our previous study.[10] The resected specimens were fixed in 10% formalin, and the entire tumor was cut into 5-mm sections. Representative slices were embedded in paraffin, cut into 3-μm sections, and stained with hematoxylin and eosin (H&E) and elastica stain to allow evaluation of serial sections for ELI status and lymphovascular invasion (Fig. 1). We used the modified resorcin-fuchsin method for the latter.[11] There is a defect of the PEL at the mesenteric attachment; therefore, we undertook elastica staining on at least 1 whole section where the tumor was closest to the peritoneal surface to confirm the continuity of the PEL. The median numbers of H&E- and elastica-stained sections were 6 (range, 2–20) and 4 (range, 2–16). We defined cases with tumor invasion beyond the PEL as ELI positive (Fig. 1C

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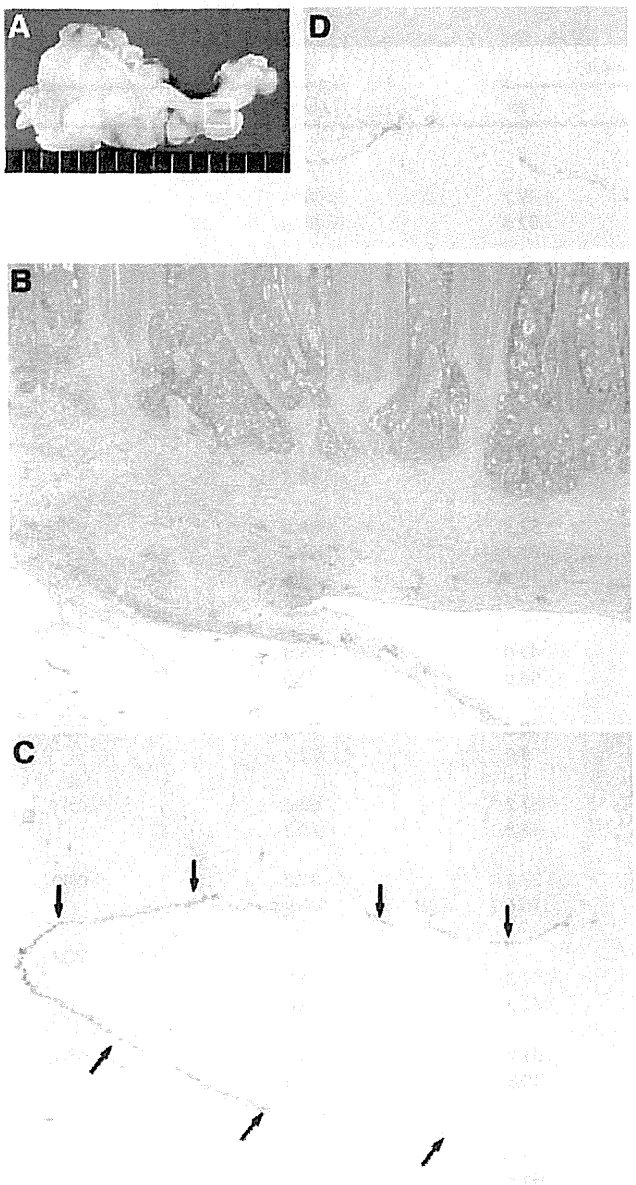

FIGURE 1. A, Cut surface of a tumor with elastic lamina invasion (ELI). Hematoxylin and eosin staining (B; ×40) and elastica staining (C; ×40; D, ×100) of the white box area in A. The peritoneal elastic lamina (PEL; arrows in C) is situated beneath the visceral peritoneum. C and D, Tumor invasion beyond the PEL represents ELI positivity.

and 1D). Continuity of the PEL in unaffected areas was confirmed regardless of the intensity of staining near the tumor. In cases with duplication of the PEL around the invasive front of the tumor, we determined cases with tumor invasion beyond the PEL to be ELI positive only when the PEL was judged the outermost layer of elastin. In cases in which the PEL had been disrupted, its estimated course was obtained by drawing a straight line between the residual PEL; only cases with invasion beyond the line were defined as ELI positive. ELI status was retrospectively evaluated by 2 pathologists blinded to the patient outcomes.

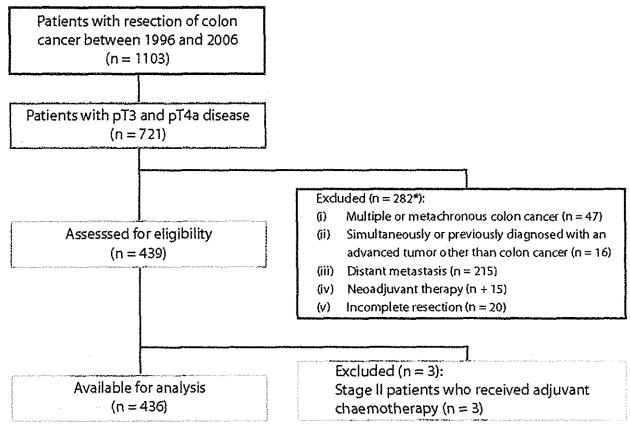

FIGURE 2. Consolidated Standards of Reporting Trials diagram of the study. *At least 1 of the criteria (i to v) was met.

Statistical Analysis

Our primary outcome measure was recurrence-free survival (RFS), defined as the time that elapsed between the date of surgery and any relapse or death from any cause. Overall survival (OS) was a secondary outcome, defined as the time from surgery to death from any cause. We chose RFS as the primary outcome to avoid the impact of treatments after recurrence on survival. Kaplan-Meier survival curves were plotted and compared using the log-rank test. Continuous variables were separated into 2 categories on the basis of their median values. All of the baseline characteristics were summarized as numbers and percentages.

To verify whether ELI status was an independent prognostic factor, we first performed multivariate Cox regression analyses for RFS. Baseline covariates included age (<65 or ≥65 years), sex (male or female), tumor size (<4.5 or ≥4.5 cm), histologic differentiation (well/moderately or poorly/mucinous), surgical technique (open or laparoscopic), lymphatic invasion (positive or negative), venous invasion (positive or negative), lymph node metastasis (positive or negative), number of lymph nodes retrieved (less than 12 or 12 or more), preoperative serum CEA level (<5 or ≥5 ng/mL), adjuvant chemotherapy (received or not received), and ELI (positive or negative).

The branch-and-bound algorithm of the Furnival and Wilson[12] variable selection procedure was applied to identify the risk factors using these candidate covariates. Next, we divided patients into all of the possible combinations based on the covariates identified in the Cox regression analyses so that their stratification would be meaningful. To establish the extent to which ELI adversely affected prognosis in NNCC, we compared the group consisting of patients with ELI-positive NNCC with groups composed of patients with node-positive CC (NPCC; stage III disease). We also applied the risk group to patients with pT3, because exclusion of pT4a patients might have influenced our proposed risk stratification. Furthermore, we evaluated how the risk group affected OS. AQ3

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TABLE 1. Patient characteristics and univariate analysis for RFS

	No. of patients (n = 436)		*RFS*	
Variable	*No.*	*%*	*5 y (%)*	*p[a]*
Age, y				
Median (range)	65.0 (26.0–92.0)			0.32
<65	208	47.7	76.2	
≥65	228	52.3	80.5	
Sex				
Male	251	57.6	76.1	0.17
Female	185	42.4	81.1	
Tumor location				
Right	146	33.5	3.7	0.08
Transverse	51	11.7	71.4	
Left	239	54.8	76.3	
Tumor stage				
pT3	393	90.1	81.0	<0.0001
pT4a	43	9.9	53.5	
Nodal status				
pN0	250	57.3	88.3	<0.0001
pN1	140	32.1	68.4	
pN2	46	10.6	54.8	
Tumor size, cm				
Median (range)	4.5 (0.6–16.5)			0.09
<4.5	196	45.0	75.0	
≥4.5	240	55.0	80.9	
Histologic differentiation				
Well/moderately	396	90.8	78.8	0.38
Poorly/mucinous	40	9.2	72.2	
Lymphatic invasion				
Negative	293	67.2	80.6	0.07
Positive	143	32.8	73.2	
Venous invasion				
Negative	102	23.4	89.0	0.002
Positive	334	76.6	74.9	
CEA, ng/mL				
Median (range)	3.9 (0.2–247.7)			0.27
<5	252	57.8	79.8	
≥5	184	42.2	76.0	
Type of surgery				
Open	267	61.2	78.0	0.84
Laparoscopic	169	38.8	78.6	
No. of lymph nodes retrieval				
Median (range)	26.5 (4.0–124.0)			0.58
<12	31	7.1	76.0	
≥12	405	92.9	78.4	
Adjuvant chemotherapy				
Received	71	16.3	78.4	0.98
Not received	365	83.7	77.2	
ELI				
Negative	254	58.3	85.1	<0.0001
Positive	182	41.7	68.8	

ELI = elastic laminal invasion; RFS = recurrence-free survival.
[a]*p* value was calculated by log-rank test (2 sided).

All of the statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). All *p* values were reported as 2 sided, and statistical significance was defined as values <0.05.

RESULTS

Patient Characteristics

A total of 436 patients with a median age of 65.0 years were enrolled (Fig. 2). Their characteristics were shown in Table 1. Tumors were located in the cecum in 26 patients (6.0%), the ascending colon in 120 (27.5%), the transverse colon in 51 (11.7%), the descending colon in 36 (8.3%), and the sigmoid colon in 203 (46.5%). Tumors were classified as stage IIA, IIB, IIIB, and IIIC in 236 (54.1%), 14 (3.2%), 165 (37.9%), and 21 patients (4.8%). Seventy-one patients (38.2%) with stage III CC received adjuvant chemotherapy after primary resection. Overall, 182 patients

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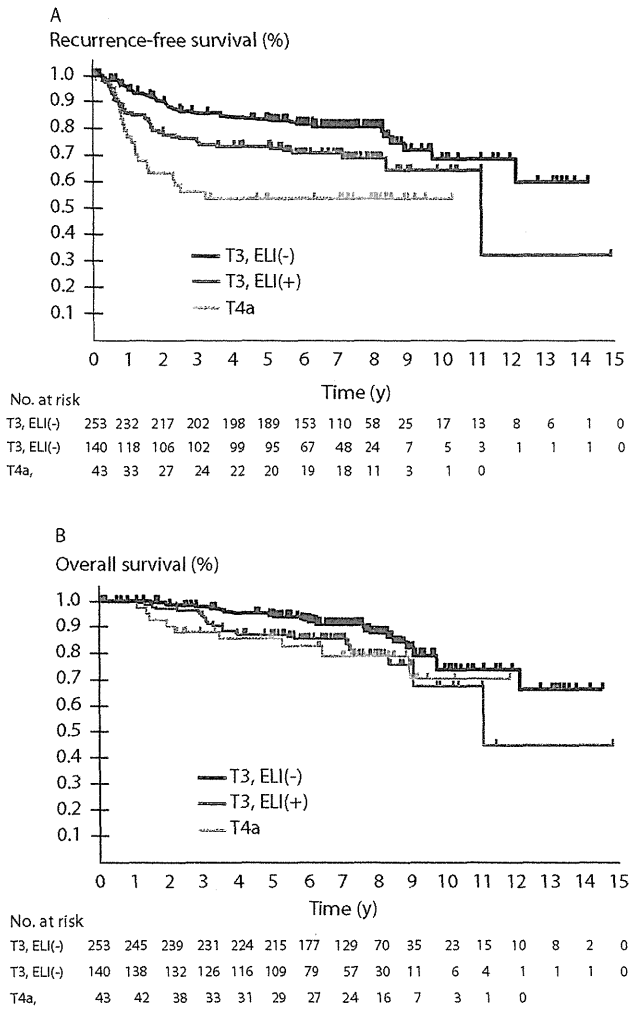

FIGURE 3. Kaplan-Meier curves depicting recurrence-free (A) and overall survival (B) based on the elastic laminal invasion status of 436 patients who underwent primary resection for colon cancer.

(41.7%) were identified as ELI positive, 140 (35.6%) of those with pT3 and 42 (97.7%) of those with pT4a disease.

Association Between ELI Status and Survival

The 5-year RFS and OS for all of the participants were 78.2% and 92.9%. The median follow-up was 7.1 years (range, 0.1–15.1 years). Of those who survived, 93.3% were followed for ≥3 years, and 88.0% were followed for ≥5 years. Tumor stage, nodal status, venous invasion, and ELI status influenced RFS (Table 1). Of the patients with pT3 disease, those who were ELI positive had a 5-year RFS of 73.8% compared with 85.0% for those who were ELI negative ($p = 0.002$) and 53.5% for patients with pT4 disease ($p = 0.02$; Fig. 3A). Tumors recurred in 95 (21.8%) of the 436 patients; the most common sites of recurrence were the liver (48 patients), lung (18 patients), and peritoneum (13 patients). The 5-year OS of ELI-positive patients with pT3 disease was 87.3% compared with 94.9% if ELI status was negative ($p = 0.02$) and 85.3% in patients with pT4 disease ($p = 0.82$; Fig. 3B). Overall, 63 patients died (14.4%): of those who died of CC, 28 were ELI positive and 14 were ELI negative; of those who died of other causes, 6 were ELI positive and 15 were ELI negative.

TABLE 2. Multivariate Cox regression analyses for RFS to assess the influence of risk factors

	RFS		
Variable	*HR*	*p*	*95% CI*
Lymph node metastasis (+)	2.96	<0.0001	1.95–4.49
Adjuvant chemotherapy (+)	0.50	0.01	0.29–0.85
ELI (+)	1.59	0.02	1.08–2.33

ELI = elastic laminal invasion; RFS = recurrence-free survival.

Multivariate Analyses

We performed Cox regression analyses on all 436 patients. For RFS, the branch-and-bound algorithm identified 3 unfavorable factors, including lymph node metastasis ($p < 0.0001$), lack of adjuvant chemotherapy ($p = 0.01$), and ELI positive status ($p = 0.02$; Table 2). Patients were divided into 6 groups based on these unfavorable factors, as shown in Table 3. We chose group 3 (node negative, ELI positive, and no adjuvant chemotherapy) as the reference value to compare with node-positive patients.

Evaluation of Prognosis

Kaplan-Meier curves for RFS in each group are shown in Figure 4A. The survival curves of group 5 (node positive, ELI negative, and no adjuvant chemotherapy) and group 6 (node positive, ELI positive, and no adjuvant chemotherapy) were almost identical ($p = 0.43$), and there was not a significant difference between group 2 (node positive, ELI negative, and received adjuvant chemotherapy) and group 4 (node positive, ELI positive, and received adjuvant chemotherapy; $p = 0.15$). There was, however, a significant difference between group 1 (node negative, ELI negative, and no adjuvant chemotherapy) and group 3 ($p = 0.001$). The RFS curve of group 3 lay between those of group 2 and group 4, both of which were composed of node-positive patients. The HR for group 1 vs group 3 was 0.49 (95% CI, 0.27–0.90), corresponding with a 51% relative reduction in the risk of recurrence. Furthermore, the HRs for groups 2 and 4 vs group 3 were 0.77 (95% CI, 0.35–1.69) and 1.36 (95% CI, 0.62–2.98).

When group 3 was compared with the other groups in terms of OS, similar trends were observed (Table 3 and Fig. 4B). The estimated OS Kaplan-Meier curve of group 3 was also between those of groups 2 and 4. The HRs for groups 2 and 4 vs group 3 were 0.88 (95% CI, 0.29–2.62) and 1.81 (95% CI, 0.61–5.41).

Findings After Exclusion of Patients With pT4a Disease

The impact of ELI status was reanalyzed using the same 6 groups after patients with pT4a disease were excluded

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TABLE 3. Comparison of 5-year RFS and OS of the 6 stratified groups

Group		n	RFS		OS	
			5-y % (95% CI)	HR (95% CI)	5-y % (95% CI)	HR (95% CI)
1	N0,ELI(−),AC(−)	166	91.1 (85.4–94.6)	0.49 (0.27–0.90)	98.1 (94.2–99.4)	0.59 (0.25–1.41)
2	N1-2,ELI(−),AC(+)	42	83.0 (67.7–91.5)	0.77 (0.35–1.69)	97.6 (83.9–99.7)	0.88 (0.29–2.62)
3	N0,ELI(+),AC(−)	84	78.3 (67.8–85.7)	1.00	91.2 (82.4–95.7)	1.00
4	N1-2,ELI(+),AC(+)	29	69.0 (48.8–82.5)	1.36 (0.62–2.98)	89.7 (71.3–96.5)	1.81 (0.61–5.41)
5	N1-2,ELI(−),AC(−)	46	57.7 (41.9–70.6)	1.92 (1.03–3.57)	82.0 (67.1–90.5)	2.10 (0.88–5.01)
6	N1-2,ELI(+),AC(-)	69	55.9 (43.3–66.7)	2.36 (1.36–4.11)	79.5 (67.3–87.6)	2.64 (1.20–5.81)

N = nodal status; ELI = elastic laminal invasion; AC = adjuvant chemotherapy; RFS = recurrence-free survival; OS = overall survival.

T4 (Table 4). The 5-year RFS for group 3 excluding those with pT4a disease (group 3′) was significantly worse than that for group 1′ (group 1 excluding those with pT4a disease; 81.1% vs 92.9%; $p = 0.003$). The RFS curve of group 3′ was similar to that of groups 2′ (group 2 excluding those with pT4a disease) and 4′ (group 4 excluding those with pT4a disease; group 3′ vs group 2′, $p = 0.61$; group 3′ vs group 4′,
F5 $p = 0.83$; Fig. 5A). The OS curve of group 3′ lay below that of groups 2′ and 4′ (group 3′ vs group 2′, $p = 0.41$; group 3′ vs group 4′, $p = 0.98$; Fig. 5B).

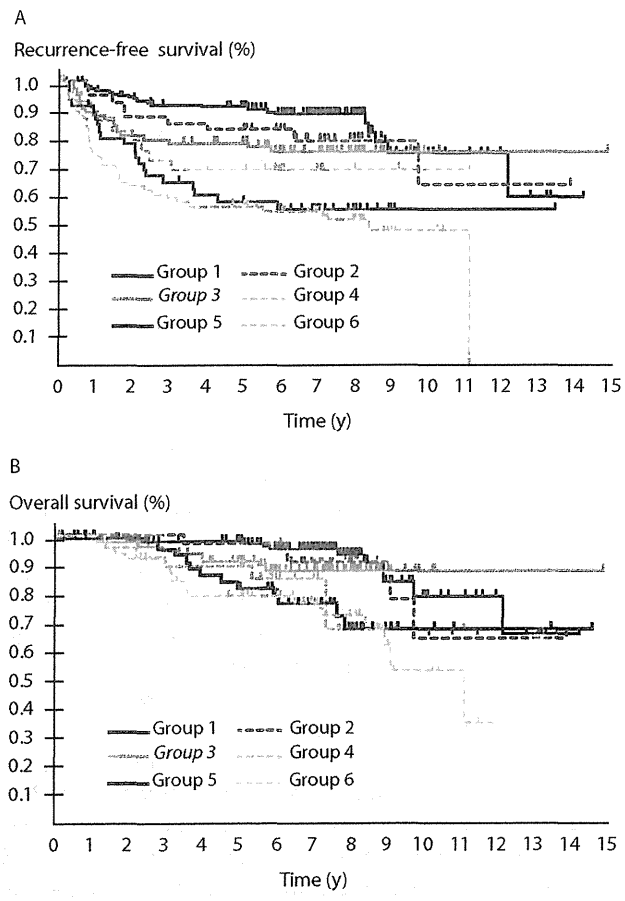

FIGURE 4. Kaplan-Meier curves depicting recurrence-free (A) and overall survival (B) of 6 groups of 436 patients who underwent primary resection for colon cancer, stratified according to elastic laminal invasion (ELI), lymph node metastasis, and adjuvant chemotherapy status. The bold line (red) represents group 3 (node negative, ELI positive, and no adjuvant chemotherapy).

DISCUSSION

ELI appears to influence outcome in patients with pT3 and pT4a CC. The RFS and OS of patients with ELI-negative NPCC (group 2) were better than those with ELI-positive NNCC (group 3). A similar trend was observed in previous reports based on the UICC 6th edition. Patients with stage IIIA (T1 to 2N1) disease had a better 5-year survival than those with stage IIA (T3N0) disease, and the Kaplan-Meier curve of patients with stage IIB (T4N0) disease lay approximately halfway between those of patients with stage IIIA and stage IIIB (T3-4N1) disease.[13,14] Whether the favorable outcome of patients with stage IIIA disease was because of limited tumor spread or adjuvant chemotherapy is unclear; these and our results show that some patients with stage II disease have a worse outcome than some with stage III disease.

Several studies have reported a variety of poor prognostic indicators in patients with stage II CC, including tumor necrosis,[15] perineural invasion,[15,16] male sex,[17] bowel obstruction,[17–19] tumor depth,[6,7,16–21] retrieval of less than 10 or 14 lymph nodes,[17,19] emergency presentation,[6] left colonic disease,[6] venous invasion,[20,21] lymphovascular invasion,[16,18,19,22] margin involvement,[20] differentiation pattern,[7] preoperative CEA level,[16] mucinous component of >50%,[18] tumor grade,[22] and tumor length.[22] Tumor depth and lymphovascular invasion have been identified most often. ELI status, which subdivides tumors invading beyond the muscularis propria, is also an indicator related to tumor depth. The "TNM Supplement: A Commentary on Uniform Use[23]" stated that the pT3 subclassification identified an extent of disease with a clinically relevant influence on outcome and could be used to determine the need for adjuvant chemotherapy.

There is a consensus that pT4 staging indicates a high risk of recurrence[24]; thus, the ELI status of patients other those with pT4a disease is also of great interest. The findings presented in Figure 5, from which patients with pT4a disease were excluded, show the poor prognosis of patients with ELI-positive NNCC with pT3 disease and indicate