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Original Article

Radiofrequency ablation of early breast cancer followed by delayed surgical resection – A promising alternative to breast-conserving surgery

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ABSTRACT

To examine the radiofrequency ablation (RFA) reliability in early breast cancer, we performed RFA followed by delayed surgical resection on 41 patients with invasive or non-invasive breast carcinoma less than 2 cm. MRI scans were obtained before ablation and resection. Excised specimens were examined pathologically by haematoxylin-eosin and nicotinamide adenine dinucleotide-diaphorase staining. 40 patients completed 1 RFA session, which was sufficient to achieve complete tumour cell death. Overall complete ablation rate was 87.8% (36/41). There were no treatment-related complications other than that of a superficial burn in 1 case. After RFA, the tumour was no longer enhanced on MRI in 25/26 (96.2%) cases. Residual cancer, which was suspected on MRI in 1 case, was confirmed pathologically. MRI could be an applicable modality to evaluate therapeutic effect. RFA could be an alternate local treatment option to breast-conserving surgery for early breast cancer.

Introduction

Early breast cancer treatment has evolved over the past decade. Currently, there has been a trend towards less-invasive approaches in the local treatment of breast cancer. Breast-conserving surgery has largely replaced mastectomy for primary breast cancer, as several large randomized trials have shown no survival difference between the 2 surgical options.[1–3] Conventional axillary lymph node dissection has been replaced with sentinel lymph node biopsy for clinically node-negative breast cancer, which affords improved staging and minimal morbidity.[4,5] With these fundamental changes in the breast cancer treatment strategy, there is an impetus to replace the less-invasive surgery with ablation techniques that eliminate the primary tumour without surgery. Several modalities enable minimally invasive ablation of the primary tumour, such as cryosurgery, laser ablation, thermoablation, and high-intensity focused ultrasound, but radiofrequency ablation (RFA) appears to be the most promising technique.

One major goal in breast-conserving treatment is to preserve a cosmetically acceptable breast. Since cosmetic results are related, to some extent, to the tissue amount removed, treating a tumour without resection has great appeal. Progress in detection methods, such as magnetic resonance imaging (MRI) and widespread application of screening mammography, will increase the detection of very small, non-palpable tumours, which further emphasizes the need for minimally invasive methods to achieve local tumour destruction. RFA is gaining acceptance as a treatment modality for several tumour types, but not yet for primary breast cancer, as there is yet insufficient evidence for its use as a standard therapy, in particular with regard to complete tumour cell death within the whole ablated area.

The current study was undertaken to determine the feasibility of treating early breast cancer with RFA and to evaluate tumour cell death and marginal clearance of ablated area by pathological study. Goals of this study were to examine the RFA reliability as a local treatment option in early breast cancer patients instead of breast-conserving surgery.

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Materials and methods

Enrolment

Forty-one patients, with pathologically proven invasive or non-invasive breast carcinoma less than 2 cm and clinically lymph node negative, were enrolled in this pilot study, conducted between March 2007 and February 2009. Core needle biopsy or vacuum-assisted biopsy was performed to determine tumour grade, lymphovascular invasion, hormone receptor status and HER2/neu status. The other inclusion criteria were as follows: tumour easily imaged by ultrasound and lumpectomy planed as the initial treatment. Exclusion criteria included more than 1 tumour in the same breast and the presence of extensive suspicious microcalcifications surrounding the tumour mass. Patients with pacemakers, sensitivity to lidocaine or coagulopathy, or who were pregnant or lactating were also excluded. Pre-treatment evaluation consisted of a complete history and physical examination, pathological review of the carcinoma and laboratory evaluation including a complete blood count and coagulation profile. Furthermore, bilateral mammography, enhanced breast MRI and positron emission tomography-CT were performed within 2 months of RFA. This study was approved by the institutional review board at Hiroshima City Hospital. All enrolled patients were informed about this study and signed a written consent for participation.

Breast ultrasound

Bilateral breast imaging was performed to include the known tumour and surrounding breast tissue using a 7.5 mHz transducer (EUB-5500; TOSHIBA, Japan). Three-dimensional tumour measurements were performed and recorded.

Breast MRI scans

Breast MRI scans were performed before ablation and within 48 h before surgical resection. The 3-T system (Signa; G.E. Medical Systems, Japan) was utilized. Patients were imaged in the prone position with a dedicated double breast coil. Axial and sagittal T1- and T2-weighted images were obtained by the following protocol: (1) axial, T1-weighted spin-echo (500–700/16–17 [repetition time in milliseconds/echo time in milliseconds]) sequence with a 32–36 cm field of view, 3 mm section, 1 mm gap, and 512 × 256 matrix for both breasts; (2) axial, T2-weighted fast spin-echo with fat saturation sequence of the affected breast, 12–18 cm field of view, 3 mm section, 1 mm gap, and 128 or 192 matrix; and (3) sagittal T1-weighted spin-echo with fat saturation sequence after the intravenous gadodiamide administration (0.5 M, Omniscan; Nycomed, Japan). A 20 ml gadodiamide bolus was administered, regardless of body weight, followed by a 20 ml physiological saline bolus. Imaging was initiated during saline injection.

Radiofrequency ablation

RFA was performed under either general anaesthesia or local anaesthesia and sedation. In the local anaesthesia group, intravenous sedation with midazolam titrated doses were administered in preparation for RFA. Under local anaesthesia and sedation, sentinel lymph node biopsy was first performed, then, under ultrasound guidance, 0.5% lidocaine was injected around the tumour. For analgesia, a sufficient volume of lidocaine injected over the pectoralis major is important. A small skin incision was made with a number 11 surgical blade. A 3 cm Cool-Tip RF Needle Electrode (Valleylab, Boulder, CO, USA) was inserted at the centre of the tumour under ultrasound guidance. For prevention of skin burn, 5% glucose liquid with a higher electrical resistance than saline was injected between the skin and tumour to increase the space between. The needle electrode was attached to a 500 kHz monopolar RF generator capable of producing 200 W. Grounding was achieved by attaching 2 grounding pads to the patient's thighs before the procedure. Tissue impedance was monitored continuously using circuitry incorporated in the generator. Radiofrequency energy was applied only once not exceeding 15 min. Power was set at 5 W and increased by 10 W intervals every 1 min until a rapid increase in impedance occurred (so-called roll-off). For prevention from skin burn, a sterile ice bag was placed on the skin over the ablated area. The core temperature of the ablated area was measured immediately after roll-off. Under general anaesthesia, the abovementioned procedure was performed but without using lidocaine and midazolam.

Surgery

Breast-conserving surgery (Bp 1.5 cm) was performed immediately after RFA (immediate surgical resection) under general anaesthesia or 1–2 months after RFA (delayed surgical resection) under local anaesthesia.

Pathological evaluation

After the specimen removal, pathological evaluation with haematoxylin-eosin (HE) staining was performed to evaluate the therapeutic effect according to the response criteria of the Japanese Breast Cancer Society[6] and to estimate the tumour size and marginal status. Moreover, to accurately evaluate tumour cell death, histochemical analysis of tumour viability with nicotinamide adenine dinucleotide-diaphorase (NADH) staining was performed.[7]

Follow up

Decisions regarding adjuvant chemotherapy or hormonal therapy were made based on the pre-treatment tumour size measured by breast MRI. Axillary lymph node metastasis was determined by sentinel lymph node biopsy results. Furthermore, prognostic indications such as estrogen receptor status, progesterone receptor status, HER2/neu status, lymphovascular invasion and grade were determined by pre-treatment core biopsy. According to each patient's risk category, adjuvant therapy was administered in all patients. Whole breast irradiation was also performed in every case.

Results

Patient characteristics

Of the 41 patients in this pilot study, 9 initially underwent breast-conserving surgery immediately after RFA under general anaesthesia (immediate surgical resection). RFA was subsequently performed under local anaesthesia and sedation in the remaining 32, following which breast-conserving surgery was performed under local anaesthesia 1–2 months after RFA (delayed surgical resection). All but 1 patient completed 1 RFA session. Patient characteristics are summarized in Table 1 (median tumour size as assessed by enhanced MRI scan, 13 mm [range, 5–18 mm]; median volume of 0.5% lidocaine administered, 42 ml [range, 32–55 ml]; median RFA application time, 9 min [range, 6–15 min]; median tumour core temperature immediately after RFA, 85 °C [range, 64–100 °C]). There were no treatment-related complications other than that of a superficial burn in 1 case right above the ablated area.

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Table 1
Characteristic of patients and primary tumour characteristics ($n = 41$).

	No. of cases
Age (years)	
Range	38–92
Median	59
Tumour size on MRI	
Median (mm)	13
< 10 mm	6
10 mm >=	35
Histology	
IDC	36
DCIS	5
Tumour grade	
1	26
2	3
3	2
ER	
+	38
–	3
PgR	
+	35
–	6
HER2	
+	1
–	40
Anaesthesia	
General	9
Local	32
Ablation time (minutes)	
Range	6–15
Median	9
Core temperature (°C)	
Range	65–100
Median	85
Complication	
Superficial skin burn	1
None	40

IDC, invasive ductal carcinoma.
DCIS, non-invasive ductal carcinoma.

Breast MRI imaging

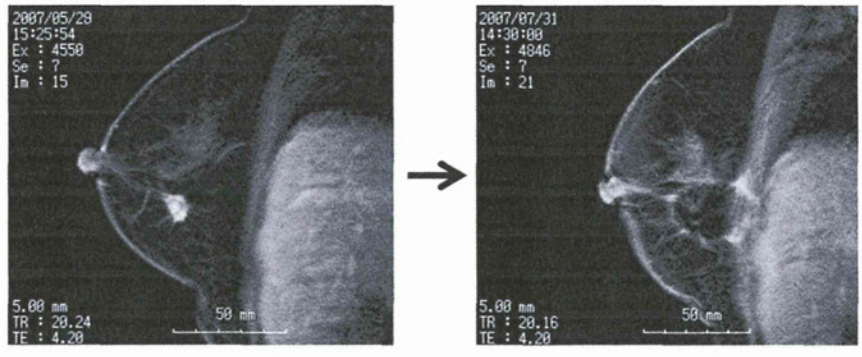
On post-RFA MRI scans, 25/26 studies (96.2%) in which the patient had pre-RFA enhancement displayed no residual enhancement of the breast lesion. In 1 case (3.8%), in which intolerable pain prevented completion of 1 RFA session, post-MRI scans demonstrated residual enhancement consistent with residual invasive and intraductal tumour, which was confirmed histologically. Therefore, a post-ablation MRI scan appears to predict therapeutic effect by RFA for breast cancer. An ablation zone, characterized by altered signal intensity and architectural distortion, with a minor degree of peripheral enhancement was easily visible in all cases. This ablation zone measured 3.0–6.1 cm at its greater diameter (median, 3.7 cm) and 1.8–5.5 cm at its lesser diameter (median, 2.5 cm). We termed this peripheral enhancement the protein degenerative ring, within which NADH staining demonstrated complete cell death. Representative pre- and post-RFA MRI scans demonstrating successful ablation and the protein degenerative ring are shown in Fig. 1. Residual cancer, which was suspected on MRI in 1 case, was confirmed pathologically (Fig. 2).

Pathological evaluation

HE staining of the ablated lesion removed immediately after RFA could not demonstrate complete tumour cell death, because cancer cell was diagnosed as viable cell only by HE staining. According to the response criteria of the Japanese Breast Cancer Society,[6] no pathological complete response (Grade 3) was observed in specimens removed immediately after RFA; however, it was observed in 4 (12.5%) specimens removed by delayed surgical resection. As times elapses after ablation, tumour cell death in a tissue sample by delayed surgical resection could be more easily diagnosed than in resection immediately after RFA. However, even in delayed surgical resection specimens, HE staining alone could not reveal all pathological complete cell death (Table 2). Therefore, to evaluate more accurate tumour cell death, NADH staining was performed in specimens from 12 patients, in all (100%) of whom no viable cancer cells (i.e., complete cell death) within the whole ablated area and surgical margins were demonstrated. Of these 12 cases, only 2 showed complete pathological response by HE staining (Table 3). Therefore, NADH staining is indispensable for evaluating tumour cell death, even in delayed surgical resection specimens. The macroscopic and histological findings are shown in Fig. 3. In 5 cases, complete histological ablation could not be achieved, with only non-invasive components remaining in 4 cases. Complete ablation was indicated on imaging examination in these 4 cases, yet pathological evaluation revealed residual non-invasive ductal cancer outside the degenerative protein ring. This may indicate the limitations of imaging-based diagnosis (in particular with regard to the extent of ductal spread, accurate diagnosis of which is not easy). Invasive and non-invasive components were found in 1 case (Fig. 2), where uncontrolled pain resulted in treatment failure. Adequate analgesia is also essential for successful ablation. Overall, a complete ablation rate of 87.8% (36/41) was observed, based on the findings of HE and NADH staining.

Discussion

Various thermal ablation treatments have been attempted for breast cancer, including cryosurgery,[8] laser ablation,[9] MR-guided



(1) Before RFA **(2) 1.5 Months after RFA**

Fig. 1. Enhanced MRI scans demonstrate successful RFA ablation. An irregular, enhancing lesion is observed in the pre-RFA image. After RFA, the tumour is no longer enhanced. A zone of ablation within the protein degenerative ring is demonstrated.

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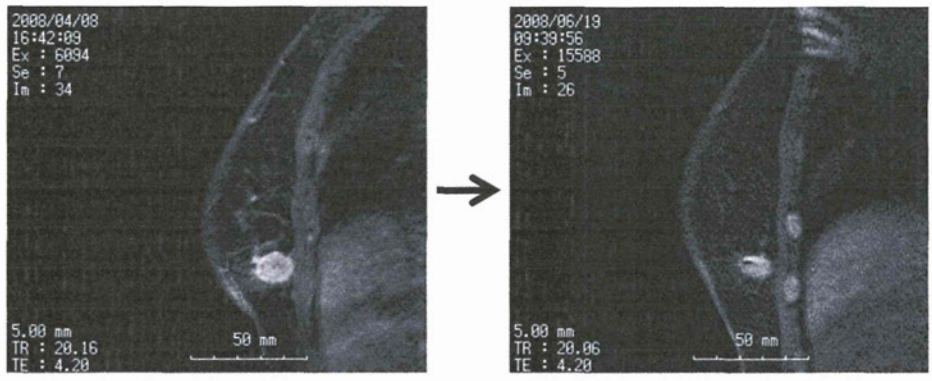

Fig. 2. The post-RFA MRI demonstrates residual enhancement consistent with a residual invasive and intraductal tumour, which was confirmed histologically.

high-intensity focused ultrasound[10] and RFA. Although each of these offers theoretical advantages, each also carries significant disadvantages. Cryoablation, requiring expensive and often bulky equipment, appears to be less effective because of incomplete freezing and a subsequent high rate of residual disease. Laser ablation is not effective for larger areas and requires another probe to measure temperature. MR-guided focused ultrasound also requires very expensive and extensive equipment; moreover it takes a few hours for a single treatment.

RFA for breast cancer appears to be the most promising modality. Many investigators have attempted feasibility studies on RFA followed by resection, as shown in Table 4, whose results support RFA use in localized breast cancer treatment.[11–21]

Our study was designed to gain further evidence on RFA reliability.

This study investigated delayed surgical resection performed 1–2 months after RFA to better assess tumour cell death over the entire ablated area; most RFA feasibility studies have investigated resection performed immediately after RFA, although 1 study reported on delayed surgical resection undertaken 1–3 weeks after RFA.[11] At the beginning of our study, we also performed immediate resection after RFA, however, pathological HE evaluation failed to demonstrate tumour cell death within the ablated zone. A delay in resection facilitates more physiological assessment. Therefore, we decided to excise the ablated area 1–2 months after RFA. To our best knowledge, no report has estimated tumour cell death in specimens resected 1–2 months after RFA. In specimens examined 1–2 months after RFA, complete tumour cell death could not be demonstrated by HE staining alone, whereas this was demonstrated by NADH staining in same specimens. NADH staining is easy and reliable in this study field. Interestingly, the cell nuclei disappearance was observed both from the centre and the ablated zone periphery by HE staining, and a cell death area was clearly demarcated from the surrounding viable tissue by a band of foam cells, which we termed the protein degenerative ring. Following resection of the ablated area 6 months after RFA, all cell nuclei in that area will disappear; complete tumour cell death may be demonstrated by HE staining alone if resection is performed over 6 months after RFA.

Another feature of this study is that RFA was performed under local anaesthesia and sedation as day surgery, a protocol that was extremely well tolerated, successful in eradicating tumours and which may point the way forward. Adequate analgesia over the pectoralis major is important in RFA, and no complications occurred, apart from the 1 case where intolerable pain obviated successful completion. On post-RFA MRI scanning, this patient had residual enhancement consistent with invasive and intraductal residual tumour, which was confirmed histologically. RFA performance under local anaesthesia by day surgery is ideal for minimally invasive treatment for breast cancer, which was one of our aims.

According to a predetermined standardized algorithm, radiofrequency energy was often applied more than once in breast cancer, but several investigators have implied that a single application is sufficient.[14,15,18] Our results are concomitant with their view for achieving complete tumour cell death within the whole ablated area, and are thus significant. Excess ablation leads to side effects such as skin burn, and multiple sessions require increased analgesia levels, which run contrary to performing RFA as day

Table 2
Histological analysis of ablated area by RFA.

Resection immediately after RFA (9 cases)	Delayed surgical resection (32cases)
Grade 1a: 4 cases (44.4%)	Grade 1a: 1 case (3.1%)
Grade 1b: 1 case (11.1%)	Grade 1b: 6 cases (18.8%)
Grade 2: 2 cases (22.2%)	Grade 2: 21 cases (65.6%)
Grade 3: 0 case (0%)	Grade 3: 4 cases (12.5%)
unknown: 2 cases (22.2%)	

Evaluation by response criteria of Japanese Breast Cancer Society	
Response criteria of Japanese Breast Cancer Society	
Grade 0	No response Almost no change in cancer cells alter treatment
Grade 1	Slight response
Grade 1a	Mild response Mild change in cancer cell regardless of the area, or marked changes in cancer cell seen in less than one third of cancer cells
Grade 1b	Moderate response Marked changes in one third or more but less two thirds of tumor cells
Grade 2	Marked response Marked changes in two thirds or more of tumor cells
Grade 3	Complete response Necrosis or disappearance of all tumor cells. Replacement of all cancer cells by granuloma-like and/or fibrous tissue, In the case of complete dassapearance of cancer cells, pre-treatment pathological evidence of the presence of cancer is necessary

Table 3
Comparison of pathological evaluation by NADH and HE staining.

NADH staining	HE staining
No viable cell: 12 cases (100%)	Grade 1a: 0 case (0%)
Viable cell: 0 case (0%)	Grade 1b: 1 case (8.3%)
	Grade 2: 9 cases (75%)
	Grade 3: 2 cases (16.6%)

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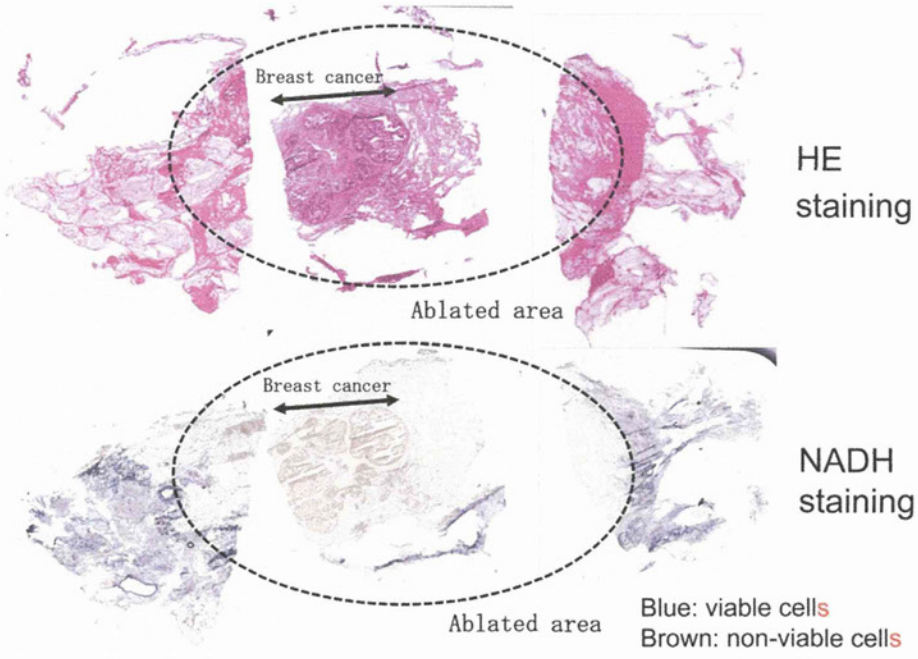

Fig. 3. NADH staining showed pathological complete cell death in the entire ablated area including surgical margin. HE staining of ablated lesion removed immediately after RFA could not demonstrate complete tumour cell death.

Table 4
Feasibility studies on radiofrequency ablation followed by surgical resection.

First Author (year) Ref.	No. of cases	T	Electrode	Application time	Power (W)	Time (min)	Complete ablation	Complications
Jeffrey (1999)[12]	5	T2-T3	LeVeen	2 times	20–60	12–28	80%	None
Izzo (2001)[13]	26	T1-T2	LeVeen	2 times	25–80	7–25	96%	Skin burn (1case)
Burak (2003)[11]	10	T1	LeVeen	Over 2 times	–	7–21	90%	None
Singletary (2003)[14]	29	T1-T2	RITA	1 time	–	30–45	86%	skin burn (1 case), Wound infection (4 cases)
Hayashi (2003)[15]	22	T1	RITA	1 time	–	–	64%	skin burn (1 case)
Noguchi (2006)[16]	10	T1	RITA	Over 2 times	–	–	100%	None
Khatri (2007)[17]	15	T1	Cool-Tip	Over 2 times	14–53	7–36	93%	Skin puckering (2 cases), Wound infection (1 case)
Medina-Franco (2008)[18]	25	T1-T2	Elektrotom	1 time	30–55	–	76%	Skin burn (3 cases), Wound infection (1 case)
Imoto (2009)[19]	30	T1	LeVeen	2 times	7–89	5–42	87%	Skin burn (2 cases), Muscle burn (7 cases)
Wiksell (2010)[20]	31	T1	NeoDynamics AB	1 time	–	6.5–11	84%	Skin burn (1case), Muscle burn (1 case), Pneumothorax (1 case)
Kinoshita (2011)[21]	49	T1-T2	Cool-Tip	2 time	5–118	–	85%	Skin burn (2 cases), Muscle burn (3 cases)
Present study	41	T1	Cool-Tip	1 time	50–110	6–15	88%	Skin burn (1 case)
Total	293	T1-T3	Various	1-over 2 times	–	–	84%	Skin burn (12 cases), Muscle burn (11 cases) Pneumothorax (1 case), Miscellaneous (8 cases)

surgery. Theoretically, one application of RFA by a 3 cm electrode can ablate 3 cm in the shorter diameter; our technique ablated 1.8–5.5 cm (median, 2.5 cm) in the shorter diameter. If the greater diameter of the tumour is 1.5 cm and the surgical margin is 0.5 cm, at minimum, the zone of ablation must therefore be 2.5 cm, and so localized tumours less than 1.5 cm are indicated for RFA.

Our findings demonstrated that a single RFA session can eradicate breast cancer less than 1.5 cm by greater diameter with no EIC (extra-intraductal component); 2 or more sessions may be effective in tumours over 1.5 cm. Paradoxically, patient selection remains a very important factor in determining the suitability of RFA for breast cancer. NADH staining demonstrated complete cell death within the ablated area (the degenerative protein ring) by MRI scanning. Thus, when performing RFA without resection, if the tumour is located within this area, core needle biopsy is unnecessary to confirm cell viability. A post-ablation MRI scan can predict the therapeutic effect by RFA for breast cancer.

RFA represents a minimally invasive treatment option for the local therapy of early breast cancer instead of breast-conserving surgery. Despite the use of various RFA procedures, the overall total ablation rate in the literature is 84% (Table 4).[11–21] RFA followed by whole breast irradiation may be a promising protocol for the local control of breast cancer. To confirm that RFA is an alternative to breast-conserving surgery, a randomized control clinical trial is indispensable for comparing the 2 treatments.

Conclusion

We found that RFA for breast cancer could be safely applied in an outpatient setting with good patient tolerance, and that only 1 RFA session could achieve total tumour cell death within the whole ablated area. RFA is a promising, minimally invasive alternative to breast-conserving surgery for local treatment in women with small ($\leq$1.5 cm) breast cancer.

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Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Diverting stoma in rectal cancer surgery. A retrospective study of 329 patients from Japanese cancer centers

Akio Shiomi · Masaaki Ito · Norio Saito · Masayuki Ohue · Takashi Hirai · Yoshiro Kubo · Yoshihiro Moriya

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Abstract
Background A diverting stoma (DS) has been constructed for many patients with low anterior resection (LAR), but it is still controversial whether DS can prevent anastomotic leakages. The aim of this study was to investigate the risk factors of anastomotic leakage including DS construction, and to evaluate the clinical course affected by DS according to the necessity of urgent abdominal reoperation for anastomotic leakage.

Patients and methods This was a retrospective analysis of 329 middle or lower rectal cancer patients who underwent LAR with mechanical reconstruction using circular staplers. Clinical data were collected from five cancer centers in Japan.

Results The overall anastomotic leakage rate was 10.0% (33 of 329). We experienced one mortality in this series (0.3%; 1/329). Clinical factors associated with DS construction included tumor location, operation time, intraoperative bleeding, lateral lymph node dissection, simultaneous resection of other organs, and the level of anastomosis, respectively.

On univariate analysis, high ligation of the inferior mesenteric artery had a significantly high leakage rate, but not on multivariate analysis. DS construction had no connection with the overall leakage rate. Concerning the clinical course affected by DS, the frequency of urgent reoperation was significantly increased in patients without DS compared with those with DS, 11.1% and 54.2%, respectively ($p=0.04$).

Conclusions LAR was the safe and preferred option for rectal cancer patients with very low mortality and an acceptable leakage rate. DS did not have a relationship with overall anastomotic leakage, but did seem to mitigate its consequences and reduce the requirement for urgent abdominal reoperation.

Keywords Rectal cancer · Anastomotic leakage · Diverting stoma · Defunctioning stoma · Low anterior resection

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Introduction

Anastomotic leakage is a major problem in rectal cancer surgery, because a sphincter-preserving operation has become standard for many rectal cancer patients. A

temporary diverting stoma (DS) has been constructed for many patients in low anterior resection (LAR). But the indication of DS construction for patients without intraoperative adverse events has not been clarified for a long time. Theoretically, DS was constructed to divert the fecal stream from anastomotic sites, and to protect fragile anastomotic sites. But it remains unproven whether diverting the fecal stream in itself directly prevents leakage. Several retrospective studies showed that the absence of DS was a risk factor for leakage in LAR, whereas others did not. Therefore, it is controversial whether DS can prevent anastomotic leakage. Although recent randomized studies [1, 2] and meta-analyses [3, 4] have shown that DS reduced the incidence of symptomatic leakage in LAR for rectal cancer, there is still limited evidence as to the impact of DS on leakage. Moreover, there have been few analyses about this issue in multicenter studies with a large number of patients from Japan.

The aim of this study was to investigate the risk factors of anastomotic leakage including DS construction, and to evaluate the clinical course affected by DS according to the necessity of urgent abdominal reoperation for such leakage using data collected from five cancer centers in Japan.

Patients and method

Patients

We reviewed the clinical data from five cancer centers in Japan which participated in the "Studies on the standardization for diagnosis, treatment, and follow-up of colorectal cancer patients", sponsored by Grant-in-Aid 18-2 for Cancer Research from the Ministry of Health, Welfare and Labor of Japan. All data on patient demographics, comorbidities, and the histological results were investigated retrospectively from the clinical records of each hospital.

From 2002 to 2004, a total of 329 consecutive patients with primary rectal cancer underwent LAR, and were investigated in this series. LAR was performed on patients with middle or lower rectal cancer, and reconstructions were done using circular staplers. Coloanal anastomosis using the hand-sewn technique was excluded from this study. Patients with subtotal colectomy, total proctocolectomy, abdominoperineal resection, Hartmann's procedure, or with pull-through procedures were also excluded.

Surgical procedure

The inferior mesenteric artery (IMA) was divided either at its origin or below the origin of the left colic artery (LCA). High ligation of IMA was defined as dividing IMA at its origin, while low ligation was defined as dividing IMA below the origin of LCA. For oncological lymph node dissection, we classify regional lymph nodes into three groups: perirectal, intermediate, and main lymph nodes. Perirectal nodes are lymph nodes in the mesorectum along the superior rectal artery. Intermediate nodes are lymph nodes along IMA between the origin of the left colic artery and the origin of the terminal sigmoid artery. Main nodes mean the lymph nodes along the IMA proximal to the origin of the LCA [5]. Lymph node dissection for UICC stage I is complete dissection of perirectal and intermediate lymph nodes, that is, low ligation without lymph node dissection around the root of IMA. Lymph node dissection for stage II, III, and IV is complete dissection of all regional lymph nodes, that is, high or low ligation with lymph node dissection around the root of IMA [6].

After total mesorectal excision or tumor-specific mesorectal excision [7], we performed rectal irrigation, while clamping the anal side of the tumor. The rectum was then divided transversely or vertically [8]. After that, we usually added lateral lymph node dissection for patients diagnosed with stage II, III, and IV [9]. Although the extent of lymphadenectomy for stage IV is still debatable, in the case that every distant metastasis (stage IV) was resectable, we perform full lymph node dissection.

Reconstruction was done using a circular stapler. Most anastomoses were straight, and colonic J pouch or transverse coloplasty pouch was sometimes used at the discretion of the operating surgeon. Intraoperative leakage test by transanal instillation of fluid or air was performed depending on the surgeon. Pelvic drain was used routinely.

Indication of DS construction

No clear applicable criteria for DS construction were stipulated in the present study. The DS construction decision was made by the individual surgeon in each case.

Definition of anastomotic leakage

Anastomotic leakage was defined clinically by the presence of the following: discharge of gas, pus, or feces from the drain or wound; discharge of pus per rectum; or rectovaginal fistula. All clinically suspicious anastomotic leakages were confirmed by one or more of the following image diagnoses: contrast study; CT scan; rectoscopy. If these cases were proven not to show anastomotic insufficiency by these imaging studies, they were defined as pelvic abscess

and not as anastomotic leakage. We did not perform routine diagnostic imaging after LAR to detect anastomotic dehiscence in clinically stable patients.

Variables analyzed

Variables included in this analysis were age, gender, body mass index (BMI), bowel obstruction, tumor location, tumor invasion, adjuvant therapy, level of IMA ligation, lateral lymph node dissection, type of anastomosis (single stapling technique, SST; or double stapling technique, DST), pouch surgery, intraoperative blood loss, operating time, DS construction, synchronous resections of other organs (hepatectomies for simultaneous liver metastasis or extended surgery to adherent organs, or additional cancer resections for double cancers), tumor size, and distal resection margin of specimen.

Bowel obstruction was defined as stenosis preventing the passage of a colon fiberscope. Tumor location was classified into middle or lower rectum according to the main part of the tumor. Tumors in the lower rectum were defined as those in which the main part was located below the peritoneal reflection. Tumor location in relation to the anal verge was preoperatively measured using rigid scope or digital examination. Tumor invasion was classified according to the UICC-TNM classification (6th edition [10]) preoperatively. Tumor size and distal resection margin were measured on the specimen before fixation with formalin. The level of anastomosis from the anal verge was measured with a digital examination. But due to the retrospective nature of this study, when the data were not available, the distance was calculated from the tumor location and distal resection margin.

Statistical analysis

In the univariate analysis, the chi-squared test and Mann–Whitney test were used. After univariate analysis, variables with a p value$\leq$0.1 were selected for multivariate analysis. A multivariate analysis was performed using a binary logistic regression model. All p values <0.05 were considered statistically significant.

Table 1 Patient characteristics

Gender	
Male	215
Female	114
Age(years)	59.0±10.5 (23–87)
Tumor location (cm)	6.1±1.7 (4.0–12.0)
Bowel obstruction	
No	305
Yes	18
Missing	6
Tumor invasion	
T1,T2	108
T3,T4	215
Missing	6
Neoadjuvant chemo Tx	
No	324
Yes	5
Anastomosis	
SST	15
DST	314
High ligation	
No	142
Yes	183
Missing	4
LLND	
No	197
Yes	132
Level of anastomosis (cm)	4.1±1.4 (1.0–9.5)
Intraoperative bleeding (ml)	598±590 (10–3723)
Operating time (min)	240±104.1 (90–620)
BMI (k/m^2)	22.6±3.1 (14.1–31.2)
Tumor size (cm)	4.4±2.3 (0–12.0)
Simultaneous resection	
No	292
Yes	37
DS construction	
No	209
Yes	120

Values are number or mean±standard deviation (ranges)

DS diverting stoma, *BMI* body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Results

Patient characteristics

From 2002 to 2004, a total of 329 consecutive patients underwent LAR. Patient characteristics were shown in Table 1. One hundred and eighteen middle rectal cancer patients and 211 low rectal cancer patients were investigated in this series. Average distance from the lower edge of the tumor to the anal verge was 6.1 cm (4.0–12.0 cm). Average distance from anastomosis to the anal verge was 4.1 cm (1.0–9.5 cm).

Neoadjuvant chemotherapy was performed for five patients, but others were treated by surgery alone. Neo-

adjuvant radiotherapy or chemoradiotherapy was not performed in this series, because preoperative therapy for resectable rectal cancer was not standard in Japan.

Synchronous resections included 20 extended resections for direct invasion of adjacent organs, 13 hepatectomies for liver metastasis, and five resections of double primary cancers.

Morbidity and mortality

The overall rate of anastomotic leakage was 10.0% (33 of 329). We experienced only one mortality in this series (0.3%; 1/329). This patient died from a septic complication caused by anastomotic leakage in the case of LAR with DS 6 days after initial surgery.

Diverting stoma

A DS was constructed in 120 patients (36.5%; 120 of 329) in initial LAR, respectively. Among the colorectal surgeons participating in this study, ileostomy was major and chosen for 92 (76.7%) patients, while transverse colostomy was done for 28 (23.3%) patients.

The DS construction rate had a significant association with tumor location. DS was constructed in only 12.7% of middle rectal cancer patients, but in 48.3% of low rectal cancer patients who experienced temporary stoma at initial LAR, respectively.

Other factors found to be significantly associated with DS construction included tumor location, operation time, intraoperative bleeding, lateral lymph node dissection,

Table 2 Univariate analysis of factors related with DS construction

	Diverting stoma		Rate	*p*-value
	DS(−)	DS(+)		
Gender				
Male	130	85	39.5	0.11
Female	79	35	30.7	
Age (years)	58.8±10.7 (23–87)	59.4±10.2 (29–75)		0.42
Tumor location (cm)	6.4±1.6 (4.0–12.0)	5.9±1.7 (4.0–12.0)		0.001
Bowel obstruction				
No	195	110	36.1	0.76
Yes	11	7	38.9	
Tumor invasion				
T1,T2	71	37	34.6	0.50
T3,T4	133	82	38.1	
Neoadjuvant chemo Tx				
No	204	120	37.0	0.10
Yes	5	0	0.0	
Anastomosis				
SST	8	7	46.7	0.40
DST	201	113	36.0	
High ligation				
No	125	58	31.7	0.12
Yes	82	60	42.3	
LLND				
No	146	51	25.9	<0.0001
Yes	63	69	52.3	
Level of anastomosis (cm)	4.2±1.4 (1.0–9.0)	3.8±1.4 (1.0–9.5)		0.002
Intraoperative bleeding (ml)	505±524 (10–2985)	760±662 (17–3723)		<0.0001
Operating time (min)	231±90.6 (90–559)	318±102.7 (130–620)		<0.0001
BMI (k/m^2)	22.9±3.0 (14.1–31.2)	22.3±3.2 (15.8–30.8)		0.07
Tumor size (cm)	4.4±2. (0–12.0)	4.4±2.3 (1.0–10.0)		0.97
Simultaneous resection				
No	192	100	34.2	0.02
Yes	17	20	54.1	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

simultaneous resection of other organs, and level of anastomosis (Table 2).

Risk factors of anastomotic leakage

Clinical variables were analyzed to investigate the risk factors for anastomotic leakage (Table 3). On univariate analysis, LAR with high ligation of IMA had a significantly high leakage rate ($p<0.05$). There were increased but statistically insignificant impacts on leakage in males, bowel obstruction, massive intraoperative bleeding, and simultaneous resection of other organs.

Nine (7.5%) of 120 patients with DS had leakage, compared with 24 (11.5%) of 209 patients without DS ($p=0.25$). DS construction also had no relevance to the overall anastomotic leakage.

Risk factors of leakage limited to the LAR without DS were also investigated. As shown in Table 4, no obvious statistical significance was found with any clinical factor.

A multivariate analysis of risk factors for anastomotic leakage showed every factor including high ligation of IMA construction as not statistically significant (Table 5).

Table 3 Univariate analysis of leakage risk factors

	Leakage		Rate	*p*-value
	No leakage	Leakage		
Gender				
Male	190	25	11.6	0.19
Female	106	8	0.7	
Age(years)	58.8±10.6 (23–87)	61.1±10.0 (40–76)		0.20
Tumor location (cm)	6.2±1.7 (4.0–12.0)	6.5±1.7 (4.0–10.0)		0.31
Bowel obstruction				
No	276	29	9.5	0.16
Yes	14	4	22.2	
Tumor invasion				
T1,T2	101	7	6.5	0.12
T3,T4	189	26	12.1	
Neoadjuvant chemo Tx				
No	291	33	10.2	0.59
Yes	5	0	0.0	
Anastomosis				
SST	13	2	13.3	0.66
DST	283	31	9.9	
High ligation				
No	135	7	4.9	0.02
Yes	157	26	14.2	
LLND				
No	177	20	10.1	0.93
Yes	119	13	9.8	
Level of anastomosis (cm)	4.1±1.4 (1.0–9.5)	4.4±1.3 (1.9–7.0)		0.13
Intraoperative bleeding (ml)	573±559 (10–3365)	817±791 (40–3723)		0.06
Operating time (min)	261±102 (90–616)	273±118 (113–620)		0.70
BMI (k/m^2)	22.7±3.1 (14.1–31.2)	22.5±3.2 (16.1–27.0)		0.87
Tumor size (cm)	4.4±2.3 (0–12.0)	5.0±2.3 (2.0–11.0)		0.18
Simultaneous resection				
No	266	26	8.9	0.06
Yes	30	7	18.9	
DS construction				
No	185	24	11.5	0.25
Yes	111	9	7.5	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Table 4 Univariate analysis of leakage risk factors (without DS patients)

	Leakage		Rate	*p*-value
	No leakage	Leakage		
Gender				
Male	114	16	12.3	0.63
Female	71	8	10.1	
Age(years)	58.7±10.8 (23–87)	59.7±10.1 (40–76)		0.65
Tumor location (cm)	6.4±1.6(4.0–12.0)	6.3±1.6 (4.0–10.0)		0.61
Bowel obstruction				
No	173	22	11.3	0.64
Yes	9	2	18.2	
Tumor invasion				
T1,T2	65	6	8.5	0.28
T3,T4	115	18	13.5	
Neoadjuvant chemo Tx				
No	180	24	11.8	0.54
Yes	5	0	0.0	
Anastomosis				
SST	7	1	12.5	0.63
DST	178	23	11.4	
High ligation				
No	108	17	13.6	0.47
Yes	75	7	8.5	
LLND				
No	130	16	11.0	0.72
Yes	55	8	12.7	
Level of anastomosis (cm)	4.2±1.4 (1.0–9.0)	4.2±1.1(2.2–7.0)		0.89
Intraoperative bleeding (cm)	480±502 (10–2985)	703±650 (40–2720)		0.07
Operating time (cm)	228±88 (90–552)	248±108(113–559)		0.60
BMI (k/m^2)	22.9±3.0 (14.1–31.2)	22.7±3.1 (16.1–27.0)		0.82
Tumor size (cm)	4.3±2.3 (0–12.0)	5.0±2.4 (2.0–11.0)		0.26
Simultaneous resection				
No	171	21	10.9	0.31
Yes	14	3	17.6	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Clinical course affected by DS construction

The clinical course affected by DS was also investigated, focusing on the necessity of urgent abdominal reoperation for anastomotic leakage. Nine of 120 (7.5%) patients who underwent LAR with DS experienced leakage. Of these nine, only one patient (11.1%) needed urgent reoperation for peritonitis, and eight patients were treated conservatively. Twenty-four of 209 (11.5%) patients who underwent LAR without DS experienced leakage, and 13 (54.2%) of them needed urgent reoperation, while 11 patients were treated conservatively (Table 6). The need for reoperation was significantly increased in patients without DS compared to those with DS, 54.2% and 11.1%, respectively ($p=0.04$).

Table 5 Multivariate analysis of leakage risk factors

	p-value	Odds ratio (95% CI)
High ligation	0.17	1.9 (0.77–4.54)
Intraoperative bleeding	0.78	1.0 (0.99–1.00)
Simultaneous resection	0.12	2.2 (0.82–6.09)

Discussion

LAR was the safe and preferred option for middle or low rectal cancer patients with very low mortality and an acceptable leakage rate among the institutes participating in this study. DS did not have a statistically significant

Table 6 Clinical course affected by diverting stoma

DS in initial LAR		Leakage		Conservative therapy	Urgent operation	Rate of urgent operation	
			%			%	
DS(+)	120	9	7.5	8	1	11.1	p=0.04
DS(−)	209	24	11.5	11	13	54.2	

relationship with the overall leakage rate. Although we cannot conclude the value of DS in terms of leakage prevention from this retrospective study, DS did seem to mitigate the consequences of leakage and reduce the need for urgent abdominal reoperation for leakage. There have been few reports about this issue in multicenter studies with a large number of patients from Japan.

With the advances in surgical procedures and devices in recent decades, sphincter-preserving surgery has become the treatment of choice for rectal cancer patients. In addition, simple and easy reconstruction has become possible thanks to circular stapling devices, even in low-level anastomosis within a narrow pelvis.

However, anastomotic leakage is still a major problem in rectal cancer surgery, sometimes resulting in severe morbidity or mortality. Since stapled anastomosis developed in the 1970s, the mortality of sphincter-preserving operations has decreased. In 1975, Fain et al. [11] reported their experience of mechanical suturing in 165 rectal cancer patients with a mortality of 2.4%. Now, symptomatic anastomotic leakage has been reported to occur in 5% to 20% of cases [12–20], and when present, the associated risk of postoperative mortality is increased to between 6% and 22% [15]. The present study encountered very low mortality (1/329; 0.3%), which is not inferior to the 0.8% recently described [2]. Our result shows the obviously improved safety of LAR using mechanical anastomosis in the Japanese cancer centers participating in this study.

Several risk factors for anastomotic leakage have been reported [12–20], and the relationship between DS and leakage was discussed in many retrospective or non-randomized prospective studies. Wong et al. [21] reported no statistical difference between patients who were defunctioned (3.8%; 28/742) and those who were not (4%; 13/324). So, they concluded that DS did not reduce the postoperative leak rate. They also concluded that a stoma carried a certain morbidity and also added to the cost of the entire operation, so it should not be performed routinely. On the other hand, Peeters et al. [18] reported that the absence of DS was significantly associated with a higher leakage rate: 43 (8.2%) of 523 patients with DS had leakage, compared with 64 (16.0%) of 401 patients without DS (p<0.001). In the present study, DS construction had no association with the overall anastomotic leakage rate. This reflects our low leakage rate in cases without DS (11.5%; 24 of 209). This rate is comparable to the leakage rate in cases with DS in a randomized controlled trial by Matthiessen et al. (10.3%; 12 of 116) [1].

Although absence of DS was not a risk factor of leakage in this study, because of a general selection bias of nonrandomized study including ours, we cannot conclude whether or not DS can prevent the leakage. This bias results from the selective creation of DS for the patients anticipated to undergo "risky" anastomosis by each surgeon as shown in this investigation. We can also point out another bias, namely that clinically unapparent leakages might have been missed in either group because no systematic assessment of the anastomosis for clinically stable patients was performed in the present study.

Only four randomized control studies sought to investigate the association between DS and leakage [1, 2, 22, 23]. Matthiessen et al. [1] reported the result of intraoperative randomization of a patient undergoing LAR for rectal cancer within 15 cm from the anal verge, and anastomosed within 7 cm. 10.3% (12 of 116) of patients with defunctioning stoma (n=116) had symptomatic leakage, against 28.8% (33 of 118) of those without stoma (n=118). They concluded that defunctioning stoma significantly decreased the rate of symptomatic leakage and was therefore recommended in LAR for rectal cancer. Pakkastie et al. [22] and Graffner et al. [23], on the other hand, could not find any statistical difference between the two groups in their randomized studies comprising 50 and 38 patients, respectively. But due to the small sample, no firm conclusion could be made. So, it is still controversial whether DS can prevent anastomotic leakage. The problem is the limited evidence about this issue. The value of DS in preventing leakage should be evaluated by more prospective studies in the future. And prospective, randomized studies are also warranted to address this issue.

Other reported risk factors include male gender [13–16], level of anastomosis [12–15], previous radiation therapy [13, 14], absence of pelvic drainage [18], poor bowel preparation [12], blood transfusion [12], immunosuppression, and underlying vascular insufficiency. Among these risk factors, male gender and level of anastomosis were widely accepted as significant for leakage. In the present study, there were increased impacts on leakage in male gender, bowel obstruction, massive intraoperative bleeding, and simultaneous resection of other organs. Although statistical significance was not reached, these factors were

comparable to those in previous reports. In the present investigation, due to the retrospective nature of the study design, the level of anastomosis was calculated from the tumor location and distal resection margin when data were not available. And in some patients, tumor location was measured only by digital examination and not by rectoscopy, these might introduce bias. Although the anastomotic level was not associated with leakage, this data should be evaluated with caution.

High ligation of IMA was the only leakage risk factor on univariate analysis in the present study. Lange et al. [24] systematically reviewed the literature concerning the level of ligation and concluded that preserving IMA and left colic artery was anatomically less invasive with respect to circulation and autonomous innervations of the proximal limb of anastomosis. Seike et al. [25] measured the colonic blood flow at the proximal site of the anastomosis by laser Doppler flowmetry to evaluate the influence of high ligation. They proved a significant reduction of colonic blood flow at the proximal site after clamping IMA. Our result also suggested the possibility that blood flow reduction on anastomotic sites leads to more leakage.

In the present study, we reported our low leakage rate in cases without DS (11.5%; 24 of 209). This rate is comparable to the leakage rate in cases with DS in a randomized controlled trial by Matthiessen et al. (10.3%; 12 of 116) [1]. This may have some association with our patient population that neoadjuvant radiotherapy or chemo-radiotherapy was not performed in this series. Neoadjuvant radiation therapy is considered to be a risk factor by some authors [13, 14]. Although randomized multicenter trials have shown that neoadjuvant radiation does not increase postoperative morbidity [26–28], Peeters et al. [18] retrospectively analyzed risk factors from the database of the Dutch Colorectal Cancer Group, and reported that a defunctioning stoma was constructed more often in patients who had received radiation, and that the absence of a DS was significantly associated with a higher leakage rate.

We also reported our low mortality. This reflects our low leakage rate in cases without DS and our appropriate decision of reoperation for peritonitis in cases without DS. We considered that our appropriate decision lead to low mortality rate and high reoperation rate (54.2%). In the present study, a DS constructed at the time of initial surgery obviously reduced the necessity of an urgent reoperation after overt leakage, proving the clinical benefits of DS in this regard. The important objective of DS was not to eliminate leakage but to decrease the risk of reoperation. However, DS construction did not guarantee the complete safety of LAR. In fact, we experienced one mortality in a patient with DS in this series, so complete elimination of leakage and severe septic complications was not feasible.

In conclusion, we clearly demonstrated the outstanding safety of LAR with very low mortality and acceptable leakage rate in our group. Although this retrospective study could not prove whether DS can prevent leakage itself, we found that it could mitigate the need for urgent abdominal reoperation for leakage. To define clear criteria for DS construction, a well-designed randomized control study is genuinely needed in the future.

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Postoperative Lymphocyte Percentage Influences the Long-term Disease-free Survival Following a Resection for Colorectal Carcinoma

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Objective: The aim of this study is to examine the relationship between postoperative laboratory parameters of inflammation and the disease-free survival in patients undergoing resection for colorectal cancer.
Methods: Six hundred seventy-five consecutive patients who underwent an elective resection for primary colorectal cancer from October 1999 to March 2004 were included in this study. We examined the associations between cancer recurrence and white blood cell count, lymphocyte percentage, neutrophil percentage and C-reactive protein.
Results: Lymphocyte percentage on postoperative days 3 and 7 was significantly higher in patients without recurrence than in those with recurrence. Lymphocyte percentage on postoperative day 7 differed the most between the two groups. On postoperative day 7, Stage II patients with lymphocyte percentage >15% had significantly longer survival compared with the patients with lymphocyte percentage ≤15%. A multivariate analysis showed lymphocyte percentage ≤15% on postoperative day 7 to be an independent prognostic factor, along with lymph node metastases and serosal invasion. Logistic regression analysis showed that blood loss (>250 ml) and postoperative complications were significant independent predictors of lymphocyte percentage ≤15% on postoperative day 7.
Conclusions: Lymphocyte percentage ≤15% on postoperative day 7 is an independent prognostic factor for the patients undergoing a resection for colorectal cancer.

Key words: colorectal carcinoma – lymphocyte percentage – less invasive surgery

INTRODUCTION

Surgery remains the definitive treatment for advanced colorectal cancer. However, major surgery causes significant alterations in metabolic, immune and endocrine functions. It has been well documented that major surgery alters multiple immune parameters and accelerates tumor growth (1–4). Links between cancer and inflammation have not been elucidated. In some types of cancer, inflammatory conditions are present before a malignant change occurs. The mediators and cellular effectors of inflammation are important constituents of the local environment of tumors (5). Some studies show that the presence of inflammation is correlated with poor prognosis in the patients with malignancies (6,7). However, the impact of the postoperative inflammatory response on the recurrence of cancer has not been elucidated.

Laparoscopic surgery has led to great progress in the treatment of colorectal cancer. Recently, published randomized trials comparing laparoscopic and open surgery do not show inferior oncologic results in patients who undergo laparoscopic surgery (8,9). Lacy et al. (10) report significant improvement in 3-year survival in patients with advanced stage cancer who undergo laparoscopic surgery. The better survival might be attributed to the favorable immunologic response and lower stress response in patients who have undergone laparoscopic surgery.

The prognostic value of biological markers in patients with advanced cancer has been investigated in palliative care. There is some evidence that abnormalities in certain laboratory parameters [e.g. leukocytosis, lymphocytopenia and an elevated C-reactive protein (CRP) level] have prognostic values (11). However, the prognostic values of these

parameters in the perioperative period have not yet been examined in patients undergoing potentially curative surgery.

We examined the preoperative and postoperative white blood cells (WBCs), neutrophil percentage (NEUTRO%), lymphocyte percentage (LYMPH%) and level of CRP. The aim of this study is to clarify the impact of these parameters on the recurrence of cancer.

PATIENTS AND METHODS

Patients

Patients with histologically proven colorectal cancer who had undergone a potentially curative resection and had routine laboratory findings were included in this study. We retrospectively reviewed a database of 675 patients between August 1999 and March 2004 at the National Cancer Center East. Demographic and clinical data (age, sex, tumor location, tumor stage, differentiation, carcinoembryonic antigen (CEA) level, surgical approach, operating time, blood loss and postoperative complication) were collected. Patients with an emergency operation, non-curative resection, no laboratory data or preoperative chemoradiotherapy were excluded. The surgical approach was decided with the consent of the patients after thorough discussion on the advantages and disadvantages of the approaches. Patients with large, fixed tumors with invasion to other organs were advised against laparoscopic resection.

Data Collection

Routine laboratory measurements were taken before the operation and on postoperative days (PODs) 1, 3 and 7. In all blood samples, WBC, LYMPH%, NEUTRO% and CRP were measured.

Statistical Analysis

The statistical analysis was performed using the SPSS 11.0.1 Statistical Software Package (SPSS Inc., Chicago, IL, USA). Comparisons of categorical ordinal variables were performed using the Pearson χ^2 test. The Mann–Whitney U-test was used to compare laboratory data at each time point between two groups. Survival rates were calculated with the Kaplan–Meier method, and differences between the curves were tested using the log-rank test. Factors related to survival were analyzed with the Cox proportional hazards regression model. Logistic regression analysis was used to estimate the odds ratio with 95% confidence intervals for LYMPH% $\leq$ 15%. A P value of <0.05 was considered to be statistically significant.

RESULTS

The median follow-up duration was 46.3 months. Within the observation period, 124 patients developed recurrence. We compared laboratory data (WBC, LYMPH%, NEUTRO% and CRP) from patients with recurrence and those without recurrence. WBC and NEUTRO% on PODs 3 and 7 in patients without recurrence were significantly lower than in those with recurrence (Fig. 1a and c). LYMPH% on PODs 3 and 7 in the patients without recurrence was significantly higher than in patients with recurrence (Fig. 1b). The difference in LYMPH% on POD 7 (LYMPH%7POD) was most evident between the two groups. We compared clinicopathological factors and disease-free survival according to LYMPH%7POD. The patients with $\leq$15% LYMPH%7POD were classified in the low group and those with more than 15% LYMPH%7POD were classified in the high group. The median of LYMPH%7POD was 15.8%.

The correlation between clinicopathological factors and LYMPH%7POD are shown in Table 1. LYMPH%7POD was significantly correlated with gender ($P = 0.01$), tumor location ($P < 0.01$) and tumor stage ($P < 0.01$). Disease-free survival was significantly higher ($P < 0.01$) in the LYMPH%7POD $>$ 15% group than in the LYMPH%7POD $\leq$ 15% group (Fig. 2). Three-year survival rates in patients with LYMPH%7POD $\leq$ 15% and in those with LYMPH%7POD $>$ 15% were 70.7 and 85.1%, respectively. More patients with advanced stage cancer had LYMPH%7POD $\leq$ 15%; therefore, disease-free survival was compared according to TMN tumor stage. As shown in Fig. 3, patients with LYMPH%7POD $>$ 15% had longer survival compared with those with LYMPH%7POD $\leq$ 15% in Stage II. Only three patients with Stage I tumors had recurrence, and there was no significant difference between the two groups in Stage I. Disease-free survival in the patients with Stage III and VI tumors was longer in the LYMPH%7POD $>$ 15% group, but the difference was not statistically significant. To determine the importance of the LYHPH%7POD as a predictor of disease recurrence, a multivariate analysis using the Cox proportional hazards model was performed. The analysis identified LYMPH%7POD $\leq$ 15% as an independent prognostic factor, along with lymph node metastases and serosal invasion (Table 2).

To identify the meaning of LYMPH%7POD, we performed logistic regression analysis with adjustments for operating time, blood loss, CEA, differentiation, lymph node metastases, serosal invasion, postoperative complications and laparoscopic surgery. Table 3 shows that blood loss ($>$250 ml) and postoperative complications were significant independent predictors of LYMPH%7POD $\leq$ 15%. The extent of tumor spread, such as lymph node metastases and serosal invasion, was not a significant predictive factor.

DISCUSSION

To date, laboratory parameters, such as CRP (6,7), lymphocytopenia and leukocytosis (12,13), have been described as significant prognostic factors in patients with advanced

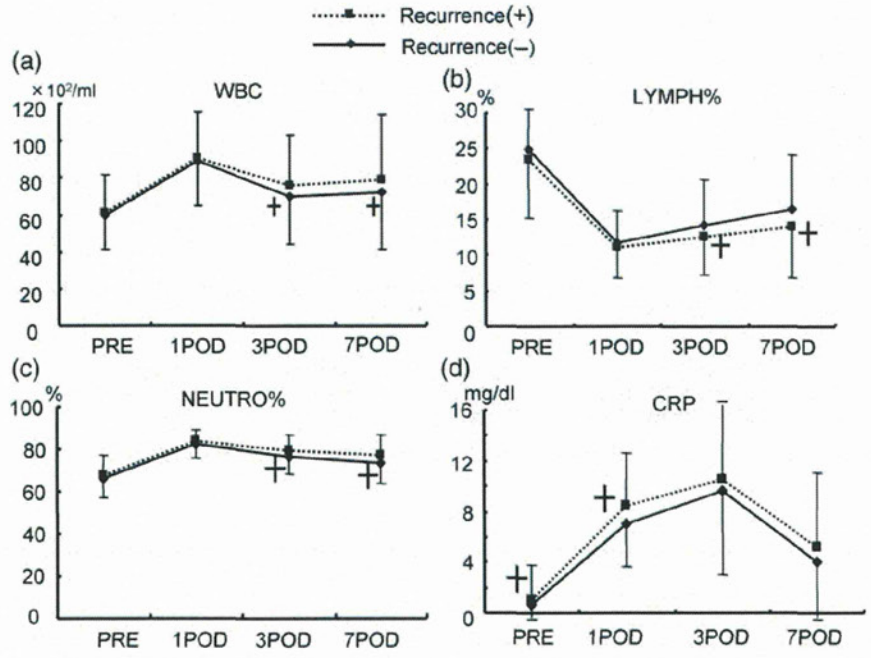

Figure 1. White blood cell (WBC), lymphocyte percentage (LYMPH%), neutrophil percentage (NEUTRO%) and C-reactive protein (CRP) in patients undergoing resection for colorectal carcinoma. Sample points were taken preoperative (PRE) and on postoperative days 1 (1POD), 3 (3POD) and 7 (7POD) ($^{+}P < 0.05$).

Table 1. The correlation between clinicopathological factors and LYMPH%7POD

	Lymph%7POD		*P* value
	>15% ($n = 248$)	≤15% ($n = 258$)	
Median age	63.6	62.6	0.31
Sex (M/F)	143/105	178/80	0.01
Tumor location			
Right side	52	39	<0.01
Transverse	23	17	
Left side	11	9	
Sigmoid	81	41	
Rectum	81	152	
Stage			
I	68	39	<0.01
II	88	81	
III	80	100	
IV	11	37	
Differentiation well or moderately	233	236	0.52
Poorly and others	9	13	

LYMPH%7POD, lymphocyte percentage on postoperative day 7.

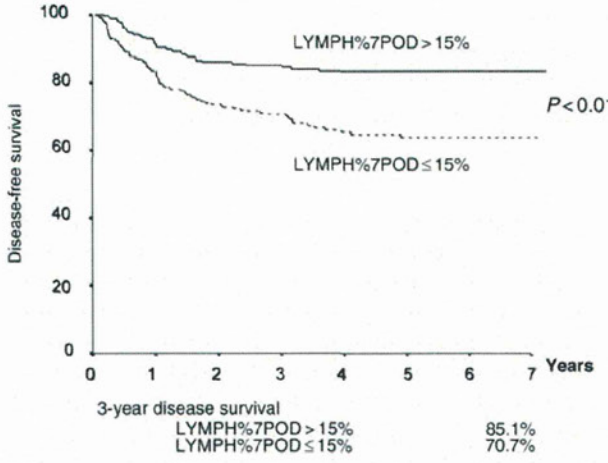

Figure 2. The disease-free survival rates of the patients with LYMPH%7POD > 15% and those with LYMPH%7POD ≤ 15%.

cancer. However, little information is available regarding the prognostic role of postoperative laboratory parameters in patients undergoing a resection of colorectal carcinoma. In this study, we evaluated whether postoperative laboratory data, such as WBC, LYMPH%, NEUTRO% and CRP, are associated with recurrence of colorectal carcinoma. This study demonstrated LYMPH%7POD ≤ 15% to significantly correlate with the recurrence of carcinoma as well as lymph node metastases and serosal invasion.

The LYMPH% is an important parameter in patients with advanced cancer (11,14,15). Some reports demonstrated that the neutrophil–lymphocyte ratio predicts survival in patients with colorectal cancer (16–18). Our results suggest that decreased LYMPH% may indicate an impaired host immune response to the tumor or inflammatory conditions that are

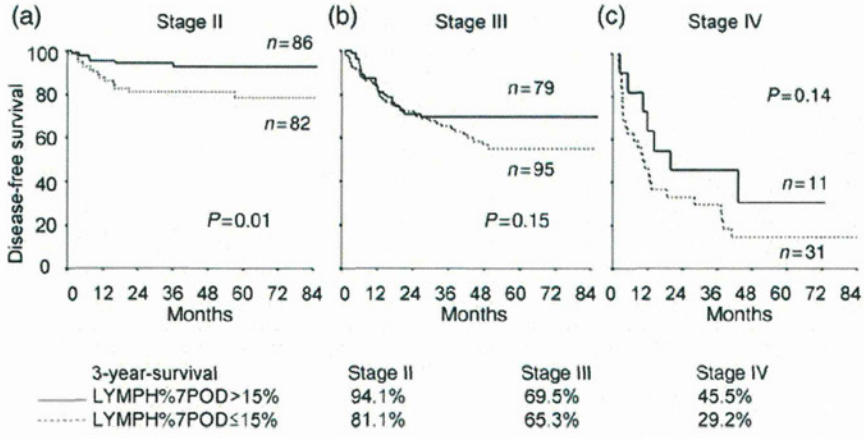

Figure 3. Comparison of disease-free survival between the patients with LYMPH%7POD > 15% and those with LYMPH7POD ≤ 15% according to TMN tumor stage.

Table 2. Multivariate analysis of risk factors affecting disease-free survival

	Hazard ratio	95% CI	*P* value
CEA >5 ng/dl	1.36	0.93–1.98	0.11
Differentiation	1.91	0.92–3.95	0.08
Lymph node metastases	5.7	2.47–13.1	<0.01
Serosal invasion	3.78	2.47–5.79	<0.01
LYMPH%7POD ≤ 15%	2.11	1.43–3.11	<0.01

CI, confidence interval; CEA, carcinoembryonic antigen.

Table 3. Multivariate analysis of clinicopathological variables for LYMPH%7POD

	Hazard ratio	95% CI	*P* value
Operating time (more than 3 h)	1.37	0.87–2.16	0.18
Blood loss (>250 ml)	2.82	1.62–4.88	<0.01
CEA >5 ng/dl	0.95	0.62–1.46	0.81
Differentiation (poorly and mucinous)	1.73	0.62–4.78	0.29
Lymph node metastases	0.75	0.47–1.20	0.23
Serosal invasion	1.34	0.89–2.03	0.17
Postoperative complication	2.89	1.90–4.39	<0.01
Laparoscopic surgery	0.64	0.37–1.11	0.11

associated with recurrence of the tumor. It is well known that lymphocytes are the most important factor in the antitumor immune system. Patients with decreased LYMPH% may exhibit a poorer lymphocyte-mediated immune response to malignancy, thereby increasing the risk of tumor recurrence. There is no correlation between LYMPH% and mode of recurrence. This study showed the difference in LYMPH% between the recurrent group and the non-recurrent group was evident on POD 7. During postoperative course, the condition of patients on POD 7 may be the most symbolic state of the recovery after surgery.

The LYMPH% shows a relative decrease in cases with inflammation. The connection between inflammation and cancer is now generally accepted. In some types of cancer, inflammatory conditions are present before a malignant change occurs.

However, it is not clear whether postoperative inflammation increases the recurrence of cancer. The relationship between surgical stress and host resistance to cancer was demonstrated in a murine model. Eggermont et al. (19) showed that a surgical procedure with entry into the abdominal cavity resulted in augmented tumor growth; conversely, a surgical incision on the animal's back did not promote tumor growth. Some authors show that anastomotic leak is associated with poor survival or local recurrence (20,21). These results suggest that acute inflammatory response may promote tumor spread and metastases. The LYMPH% may be a good indicator of systemic inflammatory response.

We demonstrated that LYMPH%7POD was significantly correlated with gender, tumor location and tumor stage. The reason for the association is speculative at present. The surgery for the patients with these variables may be more invasive and postoperative inflammatory response for these patients may be increased. We also demonstrated that blood loss (>250 ml) and postoperative complications were significant independent predictors of LYMPH%7POD ≤ 15%. Surgical techniques that minimize blood loss and postoperative complications may be associated with improved postoperative immune and nutritional status that promote long-term disease-free survival. In this study, laparoscopic surgery tented to show a decreasing LYMPH%7POD, but the decline was not significant. The LYMPH% may also be a good indicator of the immune and nutritional status in the postoperative period.

In conclusion, our data demonstrated an association between LYMPH% on POD 7 and cancer recurrence. The postoperative

LYMPH% may be a good anti-inflammatory marker and a sensitive predictor of cancer recurrence in colorectal cancer.

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Conflict of interest statement

None declared.

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