Response of liver metastases to preoperative radiochemotherapy in patients with locally advanced rectal cancer and resectable synchronous liver metastases

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Background. *No standard treatment for advanced rectal cancer with synchronous resectable liver metastases (LM) has been defined. Radiochemotherapy prior to simultaneous or staged curative resection of both primary tumor and LM is one of the treatment options available. The response of LM to radiochemotherapy has never been evaluated and, in particular, the risk for progression of LM is unknown.*

Methods. *Between 2000 and 2011, 20 patients underwent preoperative radiochemotherapy for advanced rectal cancer with synchronous limited but resectable LM. Imaging responses of LM to radiochemotherapy were analyzed on per-patient and per-lesion bases using Response Evaluation Criteria in Solid Tumors (RECIST) criteria.*

Results. *Of the patients, 20 had 41 LM; 15 of the 20 patients (75%) had rectal cancer with expected circumferential margins <1 mm on magnetic resonance imaging (MRI), and 50% had a solitary LM before treatment. Of the patients, 13 received oxaliplatin-based chemotherapy, and 7 received fluorouracil (FU)-based chemotherapy in combination with radiation. Of the 41 LM, 7 showed complete response (17%); 7 showed partial response (17%); 20 remained stable (49%); and 7 progressed (17%). Of the 25 LM treated with oxaliplatin-based chemotherapy, only 1 LM (4%) progressed. All 20 patients were suitable for resection of LM with curative intent after the radiochemotherapy.*

Conclusion. *In patients with advanced rectal cancer and synchronous limited, but resectable LM, the risk for progression of LM during radiochemotherapy is low, especially if the chemotherapy regimen contains oxaliplatin. This low risk does not compromise a curative surgical approach to LM. (Surgery 2013;■:■-■.)*

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Approximately 20% of patients with locally advanced rectal cancer have synchronous liver metastases (LM)[1] at the time of diagnosis. Treatment with curative intent can be considered for patients with resectable synchronous LM. Optimal treatment for nonmetastatic, locally advanced rectal cancer is based on preoperative radiochemotherapy (RaCT) followed by radical surgery with total mesorectal excision.[2-4] Optimal treatment for resectable LM is based on complete resection combined with perioperative oxaliplatin-based chemotherapy.[5] In patients with locally advanced rectal cancer and synchronous resectable

LM, a curative approach should, therefore, reconcile optimal treatment for both sites of disease. The design of such an approach, however, can be challenging, because optimal treatment for one tumor site should not compromise optimal treatment for the other. In this setting, no consensus on the approach to rectal cancer with resectable LM has been defined, and numerous treatment options can be proposed, including chemotherapy first, RaCT first, and upfront surgery. All these options have advantages and disadvantages and have never been compared. In 2006, French guidelines[6] recommended RaCT followed by staged or simultaneous surgery for patients with locally advanced rectal cancer and resectable synchronous LM. A potential disadvantage of RaCT is that there may be a delay in controlling metastatic disease, with the risk that the LM become unresectable if they progress during RaCT.

The aim of this study was, therefore, to evaluate response of LM to RaCT in patients with locally advanced rectal cancer and synchronous resectable LM.

METHODS

Patients. Between March 2000 and November 2011, 674 consecutive patients at our institution underwent rectal resection with total mesorectal excision with curative intent for rectal cancer. Of these 674 patients, 20 met the following inclusion criteria: locally advanced low or middle rectal cancer defined as uT3-uT4 or N+ tumor on endorectal ultrasonography[7] with a pretreatment circumferential resection margin less than 2 mm on magnetic resonance imaging (MRI); synchronous LM considered to be resectable before treatment; and initial treatment with RaCT. The resectability of LM was discussed for all patients during a multidisciplinary meeting. Resectable LM were defined as metastases that could be totally resected or treated by radiofrequency ablation during operation with clear margins (R0), while preserving remnant liver parenchyma with adequate vascular inflow (hepatic artery and portal vein) and outflow (hepatic vein). The flow chart of patients included in this series is shown in Figure 1.

Patients with extrahepatic metastatic disease, according to helical thoracic and abdominal computed tomography (CT) scans and positron emission tomography (PET) CT scans (since 2006 only) findings, were excluded. Patients in whom there was fortuitous discovery of LM during resection of rectal cancer after RaCT were also excluded.

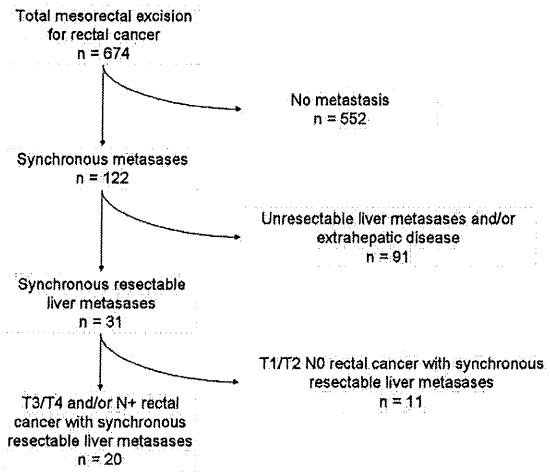

Fig 1. Flow chart of patients who underwent total mesorectal excision for rectal cancer.

Preoperative radiochemotherapy. Before 2006, decision making regarding indications of RaCT occurred on a per-patient basis during the multidisciplinary meeting. Long-course RaCT was preferred to short-course radiotherapy of 25 Gy administered over 5 days with the aim of downstaging locally advanced rectal cancer. Since 2006, our policy has been based on the French guidelines for the treatment of locally advanced rectal cancer with synchronous resectable LM; the guidelines recommend long-course RaCT.[6] In line with French guidelines, long-course radiotherapy consisted of a total dose of 45 to 50 Gy delivered in 25 fractions of 1.8 to 2.0 Gy each over a period of 5 weeks, with operation performed 6 to 8 weeks later. Concomitant preoperative chemotherapy was administered in addition to radiotherapy.[2,3] There were 3 different concurrent chemotherapy schedules. The first schedule consisted of two 5-day courses, delivered during the first and fifth weeks of radiotherapy, with 350 mg/m^2/d fluorouracil and 20 mg/m^2/d leucovorin.[2,3] The second schedule consisted of oral capecitabine (800 mg/m^2) administered twice daily on the first day of radiotherapy and 5 days per week during radiotherapy. The third schedule consisted of oral capecitabine (800 mg/m^2) administered twice daily on the first day of radiotherapy and 5 days per week during radiotherapy plus intravenous oxaliplatin (50 mg/m^2) once weekly (a total of 5 injections).[8] Starting in 2006, oxaliplatin-based chemotherapy was preferred to FU-based chemotherapy because we hypothesized that it may provide better control of metastatic disease. The radiotherapy was directed at rectal cancers only and not to LM.

Evaluation of the response of liver metastases to radiochemotherapy. For this study, tumor responses in LM were determined by imaging. The tumor responses were assessed 4 to 6 weeks after completion of RaCT by triple-phase helical CT scans with 5 mm reconstructions. Post-treatment CT images were compared to pretreatment baseline CT images, and tumor responses were graded according to RECIST criteria by 1 radiologist (MEH).[9] An objective response was defined as a partial or complete response according to RECIST criteria. For each patient, the tumor response was evaluated for all LM.

For rectal tumors, a second pelvic MRI 4 to 6 weeks after completion of RaCT was used to assess the response to treatment; to assess post-treatment T stage; and to identify the longitudinal and circumferential margins of the rectal cancer so as to determine the surgical strategy.

For both liver metastases and primary tumor, response to RaCT was assessed by imaging at the same time, 4 to 6 weeks after completion of RaCT.

Operative procedure. Between 6 and 8 weeks after the end of RaCT, patients underwent rectal resection with total mesorectal excision for rectal cancer.[10] Combined resection of rectal cancer and LM was proposed when only minor liver resection was required. In most patients, liver resection combined or not with radiofrequency was delayed and performed at a second operation. Delayed liver resection was performed after short course interval chemotherapy (2 to 4 cycles) in most patients. At laparotomy, the extent of hepatic disease was assessed by means of careful inspection, bimanual palpation, and intraoperative ultrasonography of the liver. Postoperative morbidity and mortality of the rectal and liver resections were analyzed separately, and morbidity was graded according to severity.[11]

Pathologic examination. After rectal resection, operative specimens were prepared and dissected according to the protocol described by Nagtegaal et al.[12] As reported previously,[12] involvement of the circumferential resection margin (R1 resection) was considered to have occurred if the tumor was less than 1 mm from the limit of the resection. All tumors were staged according to the TNM classification. The pathologic response of rectal tumors was also analyzed according to the Rödel grading system.[13]

After liver resection, liver samples were fixed, embedded in paraffin, and stained with hematoxylin-eosin-safran and Masson trichrome. The pathologic response was analyzed according to the classification of Blazer et al,[14] based on the percentage of residual viable tumor cells within liver lesions. This pathologic response of liver metastases could be caused partially by the short course of chemotherapy after rectal resection.

Statistical analysis. The primary endpoint was the imaging response of LM to RaCT according to RECIST criteria. Tumor response was analyzed on per-lesion and per-patient bases. For analysis of the tumor response on a per-patient basis, the least favorable response was taken into account for patients with multiple LM.

The secondary endpoint was the rate of successful treatment with curative intent, defined as complete resection of rectal cancer and LM. Univariate analysis was used to examine the relationship between progressive disease on imaging (according to RECIST) and the following variables: pretreatment size of LM; pretreatment tumor necrosis (present versus none); chemotherapy regimen (fluorouracil/leucovorin [FU/LV] versus FU/LV/oxaliplatin); number of cycles of chemotherapy; and chemotherapy-associated toxicity (present versus none). Overall and disease-free survival rates were calculated from the date of resection of all tumor sites using the Kaplan-Meier method. Quantitative data were expressed as median (range). Quantitative and qualitative variables were compared using the Fisher exact test or the Mann-Whitney U test, as appropriate.

RESULTS

Patients and tumor characteristics. Imaging revealed 41 LM in the 20 patients before treatment. The characteristics of 20 patients are summarized in Table I. Most patients (n = 12) had T3/T4 N+ rectal cancer of the lower third of the rectum. Before treatment, an R0 resection could not be planned in most patients (n = 15) because the expected circumferential margin was less than 1 mm on MRI. All patients had a limited extent of metastatic liver disease, and 10 of them had a single liver deposit. All patients received long-course RaCT: 16 patients received 45 Gy, and 4 patients received 50 Gy. Radiotherapy was completed in all but 1 patient in whom radiotherapy was stopped after 36 Gy because of severe grade IV diarrhea related to chemotherapy. Of the patients, 7 received FU-based-chemotherapy (3 oral capecitabine and 4 intravenous FU/LV), and 13 patients received oxaliplatin-based chemotherapy.

Imaging response of liver metastases to radiochemotherapy. The imaging response of LM to RaCT on a per-lesion basis is summarized in Table II. Of 41 LM, 34 showed complete or partial response or disease stabilization after RaCT, and 7 were

Table I. Characteristics of 20 patients with advanced rectal cancer (T3/T4 or node-positive) with synchronous liver metastases

	N = *20*
Median age (range)	58.5 (30–80)
Sex (M/F)	12/8
WHO status (1/2)	19/1
ASA status >3	1
Median body mass index (range)	23 (17.6–32)
Distance of rectal tumor from dentate line	
Mid rectum (5–10 cm)	4
Low rectum (<5 cm)	16
Median distance in cm (range)	3 (0–6)
Local extent of the rectal tumor	
Circumferential	11
Fixed	13
Median size of rectal tumor in cm (range)	5 (2.5–10)
Pretreatment stage of the rectal tumor	
II	4
III	16
Circumferential resection margin <1 mm on MRI	15
Liver metastases at time of diagnosis	
Unilateral/bilateral distribution	15/5
Median maximum diameter in cm (range)	2.4 (1–10)
Median number (range)	1.5 (1–5)
Liver involvement	
<30%	18
30%–50%	2
>50%	0
Radiochemotherapy-related toxicity	4
Neuropathy grade II	1
Neutropenia grade II	1
Diarrhea grade II/IV	1/1

ASA, American Society of Anesthesiology; *WHO*, World Health Organization.

scored as progressive disease. The median sum of the largest diameters of lesions on imaging was 18.3 mm (5 to 100) before treatment and 15 mm (0 to 100) after treatment, giving an overall reduction of about 10% of the total lesion diameter after RaCT.

For 25 of the 41 LM, concomitant oxaliplatin-based chemotherapy was administered in addition to radiotherapy. Of the 25, 14 LM showed an objective tumor response on imaging, and only 1 lesion progressed during RaCT. Thus, the LM showed objective responses or stabilization on imaging in most of the patients (24/25 LM) when concomitant oxaliplatin-based chemotherapy was combined with radiotherapy.

For the other 16 of the 41 LM, concomitant FU-based chemotherapy was administered with long-course radiotherapy. Of these 16, 10 LM remained stable, and 6 progressed during RaCT.

Analysis on a per-patient basis showed a complete response in 2 patients, a partial response in 2, disease stabilization in 11, and disease progression in 5. In 13 patients treated with oxaliplatin-based RaCT, complete response on imaging was observed in 2 patients, a partial response in 2, stable disease in 8, and progressive disease in 1. Of the 7 patients treated with FU-based RACT, no patients had objective responses on imaging; stable disease was observed in 3 patients; and progressive disease was seen disease in 4. No patient had objective tumor responses (complete or partial responses) in some lesions; there was associated progression in other lesions. In 1 patient, complete response was associated with partial response; in 1 patient complete response was associated with stable disease; in 1 patient partial response was associated with stable disease; and in 2 patients, stable disease was associated with progression.

The results of univariate analysis of factors predictive of progressive disease on imaging of synchronous LM during RaCT are summarized in Table III. The absence of concomitant oxaliplatin-based chemotherapy combined with long-course radiotherapy ($P = .002$) was the sole predictive factor of LM disease progression on imaging during RACT.

Imaging response of rectal cancer to radiochemotherapy. On pelvic MRI after RaCT, a partial response of the rectal tumor was observed in 10 patients, disease stabilization in 8, and progressive disease in 2. No patient had a complete morphologic response. In the 10 patients who experienced partial responses in rectal cancer after RaCT, complete responses were observed on imaging in 5 LM, partial responses in 4 LM, stable disease in 7 LM, and progressive disease in 2 LM. In the 8 patients whose rectal cancers were stable after RaCT, partial responses were observed in 3 LM, stable disease in 11 LM, and progressive disease in 5 LM. In the 2 patients who had progressive rectal cancer after RaCT, complete responses were observed in 2 LM and stable disease in 2 LM. On a per-patient basis, among the 10 patients who had partial responses in rectal cancer, 2 had complete responses, 2 had partial responses, 4 had stable disease, and 2 had progressive disease in LM. Among the 8 patients who had stable disease in rectal cancer, 5 had stable disease and 3 had progressive disease in LM. The 2 patients who progressed in rectal cancer during RaCT had stable disease in LM.

Operative results and oncologic outcome. A sphincter-saving procedure with a J-pouch coloanal

Table II. Response on cross-sectional imaging of 41 liver metastases to radiochemotherapy on a per-lesion basis

	All lesions (n = *41*)	*Treated with oxaliplatin-based chemotherapy* (n = *25*)	*Treated with FU-based chemotherapy* (n = *16*)	P
Complete response	7	7	—	<.001
Partial response	7	7	—	
Stable disease	20	10	10	
Progressive disease	7	1	6	

Table III. Univariate analysis of predictive factors of response on cross-sectional imaging of 41 synchronous rectal liver metastases during radiochemotherapy

	Tumor response/stable disease (n = *34*)	*Tumor progression* (n = *7*)	P
Median size of metastasis before treatment in cm (range)	1.9 (0.5–100)	1.6 (1–4)	.848
Pretreatment tumor necrosis	2	1	.479
Chemotherapy regimen			
FU/LV	7	6	.002
FU/LV/oxaliplatin	27	1	
Median number of cycles (range)	5 (2–5)	5 (2–5)	.879
Chemotherapy-associated toxicity	6	1	1

FU, Fluorouracil; *LV,* leucovorin.

anastomosis was performed in 15 patients. The other 5 patients underwent abdominoperineal resection for tumor that did not respond to RaCT and was less than 1 cm from the dentate line. No postoperative deaths occurred after the rectal surgeries. Of the patients, 12 experienced postoperative complications (Table IV), including a Dindo-Clavien grade IV complication in only 1 patient who required reoperation for small-bowel obstruction on postoperative day 10.

All 20 patients were suitable for a curative approach to LM including liver resection and/or radiofrequency ablation. Of the 20 patients, 4 underwent simultaneous resection of rectal cancer and LM; 1 patient was treated by radiofrequency ablation of 1 LM less than 1 cm; 1 patient was treated by radiofrequency ablation of 2 LM less than 1 cm; 1 patient had a left lobectomy (segments 2, 3) for 1 LM; and 1 patient had left lobectomy (segments 2, 3) for 3 LM. The 16 remaining patients underwent resection of LM after a median of 130 (56 to 406) days after rectal surgery. Of these 16 patients, 13 received a median number of 5 (1 to 6) cycles of interval chemotherapy. At laparotomy, liver examination found 1 LM undetected preoperatively in 1 patient, and it was resected with curative intent. Liver resection consisted of major hepatectomy (≥3 liver segments) in 10 patients and minor hepatectomy (<3 liver segments) in 6. There were no postoperative deaths after the hepatic operation, although 5 patients experienced postoperative complications (Table IV). No grade III/IV Dindo-Clavien complications were observed, and no patient required reoperation.

The median follow-up for the entire population was 24 months (4 to 69 months) from the date of resection of all tumor sites. Overall median survival was not reached at last follow-up. Overall and disease-free survival rates were 89% and 56% at 1 year and 51% and 24% at 3 years. Of the patients, 12 developed disease recurrence, including lung metastases in 4, LM in 4, and both liver and lung metastases in 4. Of 13 patients who had received RaCT containing oxaliplatin, 6 developed recurrence, and 6 of 7 patients who had received RaCT without oxaliplatin developed recurrence (P=.157).

Pathologic examination. After rectal surgery, pathologic examinations confirmed R0 resection in 16 patients and R1 resection in 4 patients. Of the 4 patients who had R1 resection of rectal cancer, 3 had abdominoperineal excision, and 1 had total mesorectal excision with coloanal anastomosis. All 4 patients had T3/T4 lesions with expected circumferential margins less than 1 mm on pretreatment imaging. Of these 4 patients, 3 received FU-based RaCT, and 1 received oxaliplatin-based RaCT.

No patient showed complete pathologic response in rectal cancer, 12 had objective pathologic responses (TRG2 to TRG3, based on the Rödel grading system), and 8 had minor (TRG1) or no pathologic responses (TRG0).

Pathologic examination was assessable for 38 LM; the 3 other LM were treated by radiofrequency

Table IV. Postoperative complications in 20 patients who underwent rectal and liver surgery

	No. patients
Rectal surgery	
No. patients with postoperative complications	12
Ileus	4
Acute urinary retention	1
Wound infection	3
Postoperative delirium	1
UTI + ileus + acute urinary retention + wound infection	1
UTI + venous catheter infection	1
UTI + wound infection	1
Liver surgery	
No. patients with postoperative complications	5
Ileus	1
Urinary t infection	1
Wound infection	1
Wound hematoma	1
Postoperative delirium	1

UTI, Urinary t infection.

ablation. A complete pathologic response was observed in 3 LM, a major pathologic response in 18 LM, and a minor response in 17 LM. Pathologic examination of the LM showed R0 resection in all but 2 patients in whom the tumor-free margin was less than 1 mm for 1 liver metastasis.

DISCUSSION

This study showed that the risk for progression of LM during RaCT is less than 20% in patients with locally advanced rectal cancer with synchronous, limited but resectable LM. In addition, this risk may be decreased to 5% by inclusion of oxaliplatin in the chemotherapy combined with radiation. This low risk for progression of LM during RaCT allowed for resection with curative intent for both the primary rectal tumor and LM in all patients. Consequently, RaCT prior to curative surgery is a feasible approach and should be considered as an appropriate option among the treatment strategies available for advanced rectal cancer with synchronous, limited but resectable metastatic liver disease.

To our knowledge, this is the first study to evaluate the behavior of synchronous, limited but resectable LM during RaCT, regardless the drug of chemotherapy used in combination with radiation. Our findings, however, are based only on a limited cohort of patients (20 in total) and LM (41 in total), so there is the possibility of type II error. These results require confirmation in a larger group of patients.

The main aim of chemotherapy during RaCT is to potentiate the effects of radiation. This chemotherapy usually consists of a low-dose FU-based regimen.[2,3] It is unclear whether such low-dose chemotherapy can control metastatic disease. Of the 16 LM treated only by 5FU or capecitabine (Xeloda) as radiosensitizers, 10 (62%) remained stable during RaCT. This observation suggests some effects of 5FU when used as a radiosensitizer in controlling LM. The response rate to oxaliplatin-based chemotherapy, however, appears to be better than that to FU-based chemotherapy in patients with colorectal LM,[5,15] leading us to hypothesize that inclusion of low-dose oxaliplatin in the chemotherapy combined with radiation may improve control of LM and possibly other metastatic diseases. As a consequence, most patients in our series were administered oxaliplatin-based rather than FU-based chemotherapy. We found that low-dose chemotherapy during RaCT was associated with objective responses in only one third of LM but nevertheless provided adequate control without progression of most of the lesions. Our findings confirmed that even at low dosage, LM are better controlled by oxaliplatin-based than by FU-based chemotherapy during RaCT. The rate of progression of resectable LM was 4% in patients who received oxaliplatin-based chemotherapy during RaCT. This compares favorably with the 7% rate reported in patients included in the European Organisation for Research and Treatment (EORTC) 40983 phase III study and treated by preoperative full-dose oxaliplatin-based chemotherapy for resectable LM.[5] Furthermore, the progression of LM during RaTC did not preclude curative treatment of LM in any of the patients. This low rate of 4% of progression, however, was observed in a group of selected patients with limited metastatic disease (only a single LM in 50% of the paients). The imaging method used in all patients in this study was helical CT scan, as is used in other institutions. It has been shown that MRI is probably the most appropriate imaging investigation to evaluate tumor response in patients treated by prolonged chemotherapy, although it is difficult to use routinely.[16] In patients receiving prolonged chemotherapy, the accuracy of CT might be decreased by the presence of changes in the liver related to chemotherapy.[17] In this study, however, the evaluation of response was made after the end of RaCT, and patients had received a maximum of 5 cycles of low-dose chemotherapy.

Although the addition of oxaliplatin to conventional, long-course RaCT has been suggested to

increase the rate of complete pathologic response in patients with advanced, nonmetastatic rectal cancer, results of recent phase III trials are controversial regarding the improvement of pathologic response associated with oxaliplatin,[8,18,19] and these studies report consistently that oxaliplatin increases the risk for toxicity.[8,18,19] In the current study, based on the Rödel grading system, the rectal cancers showed objective pathologic responses after RaCT in 60% of the patients, but none of the patients showed complete pathologic responses. A complete pathologic response to RaCT can be expected in only 15% to 20% of patients.[8,13,18,19] Our results were consistent with previous reports of 60% to 80% of patients showing objective pathologic responses to RaCT.[13,18,19] The absence of complete pathologic response in our series may be related to the initial extent of the rectal cancers; 75% of our patients had an expected circumferential resection margin of less than 1 mm on MRI before treatment. This finding is supported by the 20% rate of R1 resection and the 20% rate of non-sphincter-saving procedures despite long-course RaCT. This rate of R1 resection is consistent with previous findings after multimodality treatment including preoperative RaCT in patients with locally advanced rectal cancer.[20]

We did not observe a strong correlation between the response of rectal tumors and the response of LM to RaCT. In most patients, response was more pronounced in the primary tumor than in the LM. This observation might be related to the effect of radiation that affects only rectal cancer. In contrast, in 4 patients, responses were more pronounced in LM than in the primary tumor, which might be related to a greater sensitivity of LM to chemotherapy and especially to oxaliplatin or to the rectal cancer's being more advanced than the LM. In the absence of a strong association between the response of the rectal cancer and LM to RaCT, it would have been interesting to evaluate whether the response of rectal cancer or of the LM was more predictive of disease-free survival. Unfortunately, this analysis cannot be performed with any reliability because of the sample size.

No standard treatment strategy for locally advanced rectal cancer and synchronous resectable LM has been established. Three initial treatment options may be proposed in this setting: RaCT; chemotherapy alone; and upfront surgery of rectal cancer, LM, or both.

Upfront surgery does not appear to be appropriate in this patient population. Rectal resection of cancer without neoadjuvant treatment would lead to an increased risk for R1 resection in patients with advanced rectal cancer. In addition, perioperative chemotherapy has been shown to be associated with a lesser risk for recurrence after resection of LM.[5,21,22]

Chemotherapy first may be regarded as a valuable option in patients with rectal cancer and synchronous resectable LM. It is probably the best option in patients with extensive synchronous LM or when there is concern that liver resection might have to be greater if no systemic therapy has been given first. The main advantage of chemotherapy first is to provide early control of metastatic disease and make the reverse approach—resection of LM first—possible.[23-25] If the LM are limited and can be resected in a combination operation, short-course systemic chemotherapy followed by RaCT and simultaneous surgery is also a valuable option. The potential disadvantage of chemotherapy first is the risk for poor local control and progression of locally advanced rectal cancer that may become unresectable despite salvage RaCT. Two phase II trials report responses on cross-sectional imaging to chemotherapy without radiation in patients with locally advanced rectal cancer without metastatic disease.[26,27] In both studies, all patients were given RaCT after induction chemotherapy; it is not known whether chemotherapy alone can downstage rectal cancer with sufficient adequacy to allow R0 resection. This approach has never been evaluated in patients with advanced rectal cancer and synchronous but resectable LM.

RaCT first is also a valuable treatment option. Here, we demonstrate that RaCT provides adequate control of metastatic disease and allows a delayed resection of LM with curative intent. Most patients in our series, however, had advanced rectal cancer with limited metastatic liver disease. In addition, 13 of the 20 patients received interval chemotherapy after rectal resection, which may have contributed to the 100% rate of curative surgery of LM. We did not compare the various treatment approaches in patients with advanced rectal cancer and synchronous resectable LM. Our aim was not to define the best treatment option in these patients but rather to assess the behavior of LM during RaCT.

In conclusion, in patients with locally advanced rectal cancer and synchronous limited but resectable LM, the risk for progression of LM during RaCT is low, particularly if the chemotherapy regimen includes oxaliplatin. RaCT first provides appropriate control of the resectable LM and can be considered a

valuable treatment option in these patients. These findings require confirmation in a larger group of patients.

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An Assessment of Feeding Jejunostomy Tube Placement at the Time of Resection for Gastric Adenocarcinoma

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Background: Feeding jejunostomy tubes (J-tube) are often placed during gastrectomy for cancer to decrease malnutrition and promote delivery of adjuvant therapy. We hypothesized that J-tubes actually are associated with increased complications and do not improve nutritional status nor increase rates of adjuvant therapy.

Methods: One hundred thirty-two patients were identified from a prospectively maintained database that underwent gastric resection for gastric adenocarcinoma between 1/00 and 3/11 at one institution. Pre- and postoperative nutritional status and relevant intraoperative and postoperative parameters were examined.

Results: Median age was 64 years (range 23–85). Forty-six (35%) underwent a total and 86 (65%) a subtotal gastrectomy. J-tubes were placed in 66 (50%) patients, 34 of whom underwent a subtotal and 32 a total gastrectomy. Preoperative nutritional status was similar between J-tube and no J-tube groups as measured by serum albumin (3.5 vs. 3.4 g/dL). Tumor grade, T, N, and overall stage were similar between groups. J-tube placement was associated with increased postop complications (59% vs. 41%, $P = 0.04$) and infectious complications (36% vs. 17%, $P = 0.01$), of which majority were surgical site infections. J-tubes were associated with prolonged length of stay (13 vs. 11 days; $P = 0.05$). There was no difference in postoperative nutritional status as measured by 30, 60, and 90-day albumin levels and the rate of receiving adjuvant therapy was similar between groups (J-tube: 61%, no J-tube: 53%, $P = 0.38$). Multivariate analyses revealed J-tubes to be associated with increased postop complications (HR: 4.8; 95% CI: 1.3–17.7; $P = 0.02$), even when accounting for tumor stage and operative difficulty and extent. Subset analysis revealed J-tubes to have less associated morbidity after total gastrectomy.

Conclusion: J-tube placement after gastrectomy for gastric cancer may be associated with increased postoperative complications with no demonstrable advantage in receiving adjuvant therapy. Routine use of J-tubes after subtotal gastrectomy may not be justified, but may be selectively indicated in patients undergoing total gastrectomy. A prospective trial is needed to validate these results.

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KEY WORDS: **gastrectomy; jejunostomy feeding tubes; adenocarcinoma**

INTRODUCTION

Gastric adenocarcinoma affects approximately 20,000 individuals in the United States per year [1]. Complete resection offers the only chance for cure. The extent of gastric resection is dictated by the location of the lesion, requiring either a subtotal or total gastrectomy. After undergoing gastrectomy, patients are vulnerable to malnutrition from reduced oral intake which can increase the risk of postoperative complications and morbidity [2–5]. Adjuvant therapy is an important component of treatment for gastric cancer, and poor nutritional status can compromise the patients' ability to receive it [6,7]. The Medical Research Council Adjuvant Gastric Cancer Infusional Chemotherapy (MAGIC) trial examined the benefit of perioperative chemotherapy consisting of three cycles of epirubicin, cisplatin, and fluorouracil given before and after surgery [7]. The study found that 91% of patients were able to complete three cycles of preoperative chemotherapy, but only 42% were able to complete all six cycles [7,8]. This demonstrates the considerable difficulty that patients have in tolerating adjuvant therapy after surgery.

One approach to improve perioperative nutritional status is to administer total parenteral nutrition (TPN); however, studies demonstrate an association with increased infectious complications during the postoperative period [9]. Furthermore, the enteral route is preferred over TPN, because it prevents gastrointestinal mucosal atrophy, maintains normal enteric flora, and bolsters immune competence [10–12]. For this reason, some surgeons choose to place a feeding jejunostomy tube (J-tube) at the time of gastrectomy in an effort to optimize postoperative nutritional status. There are limited data examining the risks and benefits of J-tube placement after gastrectomy for gastric adenocarcinoma. The purpose of this study was to examine the value of J-tube placement in this clinical scenario. We hypothesized that J-tube placement is associated with increased postoperative complications, and does not substantially improve nutritional status nor increase the rate of receiving adjuvant therapy.

METHODS

A prospectively maintained gastric surgery database at the Winship Cancer Institute at Emory University was reviewed for all patients with a diagnosis of gastric adenocarcinoma who underwent resection between January 2000 and March 2011. Patients with unresectable or metastatic disease were excluded from analysis. Permission from Emory University's Institutional Review Board (IRB) was

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TABLE I. Clinicopathologic and Operative Factors of Patient Population (N = 132)

Variable	N (%)
Clinical	
Gender	
Male	67 (51%)
Female	65 (49%)
Age	63.6 (23–85)[a]
Race	
White	63 (48%)
Black	51 (39%)
Latino	4 (3%)
Asian	14 (11%)
Hypertension	58 (44%)
Diabetes	22 (17%)
Alcohol abuse	2 (2%)
Smoker	37 (28%)
Body mass index (kg/m^2), n = 36	25.7 (17.3–59.2)[a]
ASA score	3 (2–4)[a]
2	30 (23%)
3	99 (75%)
4	3 (2%)
Albumin	
Preoperative	3.5 (1.8–4.6)[a]
30-day (n = 45)	3.1 (1.2–4.4)[a]
60-day (n = 36)	3.5 (1.3–4.4)[a]
90-day (n = 53)	3.5 (1.4–4.5)[a]
30-day mortality	1 (0.8%)
Any complication	66 (50%)
Infectious complication	35 (27%)
Major complication[b]	11 (8%)
Reoperation	3 (2%)
Bleeding requiring pRBC transfusion	1 (0.8%)
Anastomotic leak	1 (0.8%)
LOS (days)	10 (2–52)[a]
30-day readmission	19 (14%)
Pathologic	
Tumor location	
GE junction	16 (12%)
Cardia	2 (2%)
Fundus	1 (1%)
Body	78 (59%)
Antrum	35 (26%)
Tumor size	4.2 (0.2–15.0)[a]
AJCC 7 T-stage	3 (1–4)[a]
1	31 (24%)
2	16 (13%)
3	39 (31%)
4	40 (32%)
Margin status	
Positive	8 (6%)
Negative	124 (94%)
Margin distance (cm)	
Proximal	3.0 (0–16.5)[a]
Distal	3.5 (0–21)[a]
Lymph node positive	76 (58%)
Number positive lymph nodes	1 (0–25)[a]
Total number lymph nodes recovered	15 (0–50)[a]
Lymphovascular invasion	40 (30%)
Perineural invasion	24 (18%)
Operative	
Operative procedure	
Total gastrectomy	46 (35%)
Subtotal gastrectomy	86 (65%)
Type of operation	
Laparoscopic	7 (5%)
Open	125 (95%)
Peritoneal drain	73 (55%)
Jejunostomy tube	66 (50%)
Operative time (min)	234 (48–567)[a]
EBL (ml)	200 (20–700)[a]

ASA, American Society of Anesthesiologists; GE, gastroesophageal; AJCC, American Joint Committee on Cancer; EBL, estimated blood loss.
[a]Median (range).
[b]Death (n = 1), sepsis (n = 4); respiratory failure (n = 4), myocardial infarction (n = 1), hemorrhage (n = 1).

obtained prior to data review, and Health Insurance Portability and Accountability Act (HIPAA) compliance was ensured.

A total of 132 patients were identified who underwent gastric resection. Patients who received a J-tube at the time of operation were noted. Relevant clinical, intraoperative, pathologic, and postoperative variables were ascertained from the patient's medical record. Total gastrectomy was defined as resection of the entire stomach, and subtotal gastrectomy as removal of anything less than a total gastrectomy. Pre- and post-operative nutritional status was measured by serum albumin (g/dL) level. Postoperative complications were defined according to the Clavien–Dindo scoring system [13].

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences 17.0 for Windows (SPSS, Inc., Chicago, IL). Chi-square analyses were used to determine the associations between nominal variables and Student's *t*-test to evaluate differences in means between two groups of continuous variables. A planned subset analysis by operation type of patients undergoing total versus subtotal gastrectomy was performed. A multivariate logistic regression analysis was performed to assess the independent association of J-tube placement with postoperative complications and rate of receiving adjuvant therapy. The multivariate model was constructed to include common clinically relevant factors such as patient age and comorbidities (ASA class), operative difficulty (blood loss), and extent of resection (subtotal vs. total gastrectomy), and tumor burden (T- and N-stage).

RESULTS

The median age of patients was 64 years (range 23–85) and 67 (51%) were male. Clinicopathologic and operative details are shown in Table I. Eighty-six (65%) of patients underwent a subtotal gastrectomy, and 46 (35%) a total gastrectomy. None of the patients underwent urgent operations for severe obstruction or life-threatening bleeding. Twenty-two (17%) patients received preoperative therapy. Ten (8%) patients underwent a multivisceral organ resection due to local tumor involvement. A D2 lymph node dissection was performed in 79% of patients and the median number of lymph nodes retrieved for all patients was 15. TPN was administered postoperatively in 13% (n = 17) of patients and six of these patients also had a J-tube placed at the time of operation; 3 of the 17 patients experienced a major complication postoperatively. All patients that underwent a total gastrectomy were studied with a fluoroscopic swallow examination postoperatively prior to initiation of oral feeding.

Jejunostomy Tube Placement

A J-tube was placed in 66 (50%) of patients, half (n = 34) of whom underwent a subtotal gastrectomy and half (n = 32) a total

TABLE IIA. Comparison of Patients With and Without J-Tube Placement in All Patients (N = 132)

Variable	Jejunostomy tube (N = 66) N (%)	No jejunostomy tube (N = 66) N (%)	*P*-value
Gender			0.38
Male	36 (55%)	31 (47%)	
Female	30 (45%)	35 (53%)	
Age	62 (23–84)[a]	64 (32–85)[a]	0.46
Race			0.39
White	29 (44%)	34 (52%)	
Black	25 (38%)	26 (39%)	
Latino	2 (3%)	2 (3%)	
Asian	10 (15%)	4 (6%)	
Hypertension	22 (33%)	36 (55%)	0.02
Diabetes	12 (18%)	10 (15%)	0.64
Alcohol Abuse	2 (3%)	0 (0%)	0.15
Smoker	19 (29%)	18 (27%)	0.85
Body mass index (kg/m^2), n = 36	26.2 (18.7–31.3)[a]	22.8 (17.3–59.2)[a]	0.37
ASA score	3 (2–4)[a]	3 (2–4)[a]	0.76
2	16 (24%)	14 (21%)	
3	48 (73%)	51 (77%)	
4	2 (3%)	1 (2%)	
Received preoperative therapy	6 (9%)	16 (24%)	0.04
Operative procedure			0.002
Total gastrectomy	32 (49%)	14 (21%)	
Subtotal gastrectomy	34 (51%)	52 (79%)	
Multivisceral organ resection	6 (9%)	4 (6%)	0.74
Operative time (min)	270 (SEM 14)	231 (SEM 15)	0.07
EBL (ml)	243 (SEM 30)	175 (SEM 14)	0.02
Grade			0.44
Well	3 (5%)	4 (6%)	
Moderate	17 (26%)	20 (30%)	
Poor	46 (69%)	42 (64%)	
Tumor (T) stage			0.88
1	16 (24%)	17 (26%)	
2	9 (14%)	9 (14%)	
3	19 (29%)	18 (27%)	
4	22 (33%)	22 (33%)	
Nodal (N) stage			0.86
0	28 (42%)	27 (41%)	
1	12 (18%)	13 (20%)	
2	15 (23%)	12 (18%)	
3	11 (17%)	14 (21%)	
AJCC 7 stage			0.94
1	21 (32%)	19 (29%)	
2	17 (26%)	18 (27%)	
3	28 (42%)	29 (44%)	
Any complication	39 (59%)	27 (41%)	0.04
Infectious complication	24 (36%)	11 (17%)	0.01
Major complication	7 (11%)	4 (6%)	0.35
Reoperation	2 (3%)	1 (2%)	0.56
Bleeding requiring pRBC transfusion	1 (2%)	0 (0%)	0.32
Anastomotic leak	0 (0%)	1 (2%)	0.32
30-day readmission	9 (14%)	10 (15%)	0.80
LOS (days)	13 (7–33)[a]	11 (2–52)[a]	0.05
Albumin			
Preoperative (n = 132)	3.5 (1.8–4.4)[a]	3.4 (2.1–4.6)[a]	0.88
30-day (n = 60)	3.1 (1.2–4.3)[a]	3.1(1.2–4.4)[a]	0.94
60-day (n = 42)	3.4 (1.3–4.4)[a]	3.3 (2.0–4.4)[a]	0.57
90-day (n = 61)	3.5 (1.4–4.5)[a]	3.3 (1.5–4.2)[a]	0.52
Received adjuvant therapy after surgery	40 (61%)	35 (53%)	0.38

pRBC, packed red blood cell; AJCC, American Joint Committee on Cancer.
[a]Mean (range). SEM, standard error of the mean.

TABLE IIB. Multivariate Analysis of Risk Factors for Increased Postoperative Complications in All Patients (N = 132)

Variable	Odds-ratio	95% CI	*P*-value
Age	1.03	0.99–1.07	0.18
ASA	1.59	0.46–5.45	0.46
Total gastrectomy	0.72	0.21–2.45	0.59
EBL	1.00	0.99–1.01	0.68
T-stage	1.06	0.62–1.79	0.84
N-stage	1.43	0.87–2.34	0.16
J-tube placement	4.79	1.30–17.66	0.02

TABLE IIC. Multivariate Analysis of Factors Associated With Increased Rate of Receiving Adjuvant Therapy in All Patients (N = 132)

Variable	Odds-ratio	95% CI	*P*-value
Age	0.95	0.92–0.99	0.008
ASA	0.25	0.08–0.77	0.02
T-stage	1.13	0.76–1.67	0.56
N-stage	1.74	1.16–2.61	0.008
Total gastrectomy	1.21	0.51–2.92	0.67
J-tube placement	1.36	0.59–3.16	0.47

gastrectomy (Table IIA). Patients undergoing a total compared to subtotal gastrectomy were more likely to have a J-tube placed (70% vs. 40%). Patients who received a J-tube were less likely to have undergone preoperative therapy (9% vs. 24%, $P = 0.04$). With the exception of hypertension, there was no difference between patients who did and did not receive a J-tube with respect to age, race, gender, ASA class, BMI, tumor grade, tumor (T) stage, nodal (N) stage, overall tumor AJCC 7 stage, presence of comorbidities, and preoperative nutritional status as measured by serum albumin level (Table IIA).

J-tube placement was associated with an increased rate of postoperative complications (59% vs. 41%, $P = 0.037$) and specifically infectious complications (36% vs. 17%, $P = 0.010$). The most common infectious complication was a surgical site infection of the main operative incision (n = 14); others included urinary tract infection (n = 9), bacteremia (n = 8), *Clostridium difficile* infection (n = 3), pneumonia (n = 3), intra-abdominal abscess (n = 1), and varicella zoster infection (n = 1). Multivariate regression analysis revealed J-tube placement to be associated with increased postoperative complications (HR: 4.79; 95% CI: 1.3–17.7; $P = 0.02$) even when accounting for patient age, comorbidities, tumor stage, intraoperative difficulty (as measured by estimated blood loss) and extent of operation (Table IIB). A trend towards increased major complications (Clavien–Dindo score III–V) was observed in patients with J-tube placement (11% vs. 6%, $P = 0.345$). J-tube placement was also associated with an increased length of hospital stay (LOS; 13 days vs. 11 days, $P = 0.050$). There was no significant difference with regards to the rate of blood transfusion, anastomotic leak, or 30-day readmission (Table IIA).

Sixty-one percent (n = 40) of patients with a J-tube placed utilized it for enteral feeding prior to hospital discharge. Postoperative nutritional status as measured by 30-, 60-, and 90-day albumin levels were similar in both groups of patients (Table IIA). There was also no difference in albumin levels between patients who received enteral nutrition compared to those who did not. There was no difference in the rate of administering adjuvant therapy; 40 patients (61%) with a J-tube placed went on to receive adjuvant therapy compared to 35 patients (53%) with no J-tube ($P = 0.38$). Multivariate regression

TABLE IIIA. Comparison of Patients With and Without J-Tube Placement in Patients Undergoing Subtotal Gastrectomy (N = 86)

Variable	Subtotal (N = 86) N (%)	Jejunostomy tube (N = 34) N (%)	No jejunostomy tube (N = 52) N (%)	*P*-value
Gender				0.28
Male	47 (55%)	21 (62%)	26 (50%)	
Female	39 (45%)	13 (38%)	26 (50%)	
Age	65.3 (23–85)[a]	62 (23–84)	63 (33–85)	0.41
Race				0.11
White	36 (42%)	11 (32%)	25 (48%)	
Black	34 (40%)	13 (38%)	21 (40%)	
Latino	3 (4%)	1 (3%)	2 (4%)	
Asian	13 (15%)	9 (27%)	4 (8%)	
Hypertension	37 (43%)	9 (27%)	28 (54%)	0.01
Diabetes	16 (19%)	8 (24%)	8 (15%)	0.34
Alcohol abuse	2 (2%)	2 (6%)	0 (0%)	0.08
Smoker	24 (28%)	9 (27%)	15 (29%)	0.81
Body mass index (kg/m^2) n = 36	26.4 (19.5–35.9)[a]	25.8 (18.7–31.3)[a]	27.7 (17.3–59.2)[a]	0.06
ASA score	3 (2–4)[a]			0.58
2	19 (22%)	8 (24%)	11 (21%)	
3	64 (74%)	24 (70%)	40 (77%)	
4	3 (4%)	2 (6%)	1 (2%)	
Any complication	43 (50%)	22 (65%)	21 (40%)	0.03
Infectious complication	22 (26%)	13 (38%)	9 (17%)	0.03
Major complication	9 (11%)	5 (15%)	4 (8%)	0.30
Reoperation	2 (2%)	1 (3%)	1 (2%)	0.76
Bleeding requiring pRBC transfusion	1 (1%)	1 (3%)	0 (0%)	0.21
Anastomotic leak	1 (1%)	0 (0%)	1 (2%)	0.42
30-day readmission	10 (12%)	2 (6%)	8 (15%)	0.18
LOS (days)	12 (2–52)[a]	13 (7–33)[a]	11 (2–52)[a]	0.25
Albumin				
Preoperative (n = 86)	3.5 (2.2–4.6)[a]	3.5 (2.2–4.4)[a]	3.5 (2.2–4.6)[a]	0.88
30-day (n = 39)	3.2 (1.2–4.4)[a]	3.3 (1.8–4.3)[a]	3.2 (1.2–4.4)[a]	0.63
60-day (n = 24)	3.6 (2.1–4.4)[a]	3.7 (3.0–4.4)[a]	3.5 (2.1–4.4)[a]	0.47
90-day (n = 38)	3.4 (1.4–4.3)[a]	3.4 (1.4–4.3)[a]	3.4 (1.5–4.2)[a]	0.78
Received adjuvant therapy after surgery	46 (54%)	19 (56%)	27 (52%)	0.72

pRBC, packed red blood cell.
[a]Mean (range).

analysis also revealed a failure of jejunostomy tubes (J-tubes) to increase the rate of receiving adjuvant therapy (Table IIC). Advanced age and ASA class were associated with a lower likelihood of receiving adjuvant therapy, while lymph node involvement was associated with receipt of adjuvant therapy (Table IIC).

Subtotal Gastrectomy and J-Tube

In a planned subset analysis of only those patients who underwent a subtotal gastrectomy (n = 86), with the exception of hypertension, there was no difference in demographics between those patients who did and did not receive a J-tube at the time of operation (Table IIIA). J-tube placement again was associated with increased postoperative complications (65% vs. 40%, $P = 0.03$) and infectious complications (38% vs. 17%, $P = 0.03$; Table IIIA). Similar to the entire cohort, multivariate analysis showed that J-tube placement was associated with increased postoperative complications (HR: 19.1; 95% CI: 2.25–163.0; $P = 0.007$), even when accounting for advanced T-stage and N-stage, as well as intraoperative difficulty as measured by estimated blood loss (Table IIIB). There was a trend in increased major postoperative complications and longer hospital stay in patients who underwent concomitant J-tube placement. Fifty-three percent (n = 18) of the 34 patients who had a J-tube utilized it for enteral nutrition prior to hospital discharge. There was no difference in postoperative albumin levels at 30, 60, and 90 days after operation (Table IIIA). The rate of receiving adjuvant therapy was similar between groups (56% with J-tube vs. 52% without J-tube, $P = 0.72$). On multivariate analysis, J-tube placement was not associated with

TABLE IIIB. Multivariate Analysis of Risk Factors for Increased Postoperative Complications in Patients Undergoing Subtotal Gastrectomy (N = 86)

Variable	Odds-ratio	95% CI	*P*-value
Age	1.04	0.98–1.11	0.17
ASA	2.06	0.35–12.17	0.43
EBL	1.00	0.99–1.01	0.74
T-stage	0.89	0.43–1.85	0.76
N-stage	2.09	1.00–4.36	0.05
J-tube placement	19.14	2.25–163.00	0.007

TABLE IIIC. Multivariate Analysis of Factors Associated With Increased Rate of Receiving Adjuvant Therapy in Patients Undergoing Subtotal Gastrectomy (N = 86)

Variable	Odds-ratio	95% CI	*P*-value
Age	0.94	0.89–0.98	0.007
ASA	0.26	0.07–1.02	0.05
T-stage	0.95	0.56–1.59	0.84
N-stage	2.25	1.25–4.03	0.007
J-tube placement	1.20	0.41–3.49	0.74

TABLE IVA. Comparison of Patients With and Without J-Tube Placement in Patients Undergoing Total Gastrectomy (N = 46)

Variable	Total (N = 46) N (%)	Jejunostomy Tube (N = 32) N (%)	No Jejunostomy Tube (N = 14) N (%)	*P*-value
Gender				0.48
Male	20 (44%)	15 (47%)	5 (36%)	
Female	26 (56%)	17 (53%	9 (64%)	
Age	61.2 (24–83)[a]	60 (24–83)[a]	59 (32–77)[a]	0.93
Race				0.80
White	27 (59%)	18 (56%)	9 (64%)	
Black	17 (37%)	12 (38%)	5 (36%)	
Latino	1 (2%)	1 (3%)	0 (0%)	
Asian	1 (2%)	1 (3%)	0 (0%)	
Hypertension	21 (46%)	13 (41%)	8 (57%)	0.30
Diabetes	6 (13%)	4 (13%)	2 (14%)	0.87
Alcohol abuse	0 (0%)	—	—	—
Smoker	13 (28%)	10 (31%	3 (21%)	0.50
Body mass index (kg/m^2), n = 36	24.4 (17.3–35.9)[a]	26.3 (19.5–30.8)[a]	25.2 (19.6–35.9)[a]	0.78
ASA score	3 (2–4)[a]	3 (2–4)[a]	3 (2–4)[a]	0.79
2	11 (24%)	8 (25%)	3 (21%)	
3	35 (76%)	24 (75%)	11 (79%)	
4	0 (0%)	—	—	
Any complication	23 (50%)	17 (53%)	6 (43%)	0.52
Infectious complication	13 (28%)	11 (34%)	2 (14%)	0.16
Major complication	2 (4%)	2 (6%)	0 (0%)	0.34
Reoperation	1 (2%)	1 (3%)	0 (0%)	0.50
Bleeding requiring pRBC transfusion	0 (0%)	0 (0%)	0 (0%)	—
Anastomotic leak	0 (0%)	0 (0%)	0 (0%)	—
30-day readmission	10 (22%)	7 (22%)	3 (21%)	0.97
LOS (days)	13 (5–30)[a]	14 (8–30)[a]	10 (5–15)[a]	0.008
Albumin				
Preoperative (n = 46)	3.3 (1.8–4.2)[a]	3.4 (1.8–4.2)[a]	3.2 (2.1–4.1)[a]	0.45
30-day (n = 21)	2.9 (1.2–3.8)[a]	2.9 (1.2–3.8)[a]	2.7 (2.0–3.3)[a]	0.47
60-day (n = 18)	3.1 (1.3–4.4)[a]	3.2 (1.3–4.4)[a]	2.7 (2.0–3.7)[a]	0.27
90-day (n = 23)	3.4 (1.9–4.5)[a]	3.5 (1.9–4.5)[a]	3.2 (2.7–3.6)[a]	0.37
Received adjuvant therapy after surgery	29 (63%)	21 (66%)	8 (57%)	0.58

pRBC, packed red blood cell.
[a]Mean (range).

an increased rate of receiving adjuvant therapy (Table IIIC). Of those patients who received adjuvant therapy after subtotal gastrectomy, 41% (n = 19) had a J-tube in place compared to 59% (n = 27) who did not.

Total Gastrectomy and J-Tube

In a similar planned subset analysis of only those patients who underwent a total gastrectomy (n = 46), there were no differences in demographics between those patients who did and did not receive a J-tube at the time of operation (Table IVA). Patients with J-tubes displayed trends towards higher postoperative complications (53% vs. 43%, $P = 0.52$), infectious complications (34% vs. 14%, $P = 0.16$), and major complications (6% vs. 0%, $P = 0.34$). Multivariate analysis did not reveal J-tube placement to be independently associated with increased complications (Table IVB). LOS was longer with J-tube placement (14 days vs. 10 days, $P = 0.008$). Sixty-nine percent (n = 22) received enteral nutrition via their J-tube prior to hospital discharge. There was no difference in postoperative albumin levels at 30, 60, and 90 days after operation (Table IVA). The rate of receiving adjuvant therapy was similar between groups (66% with J-tube vs. 57% without J-tube, $P = 0.58$), and the lack of association of J-tube placement with an increased rate of receiving adjuvant therapy persisted on multivariate analysis (Table IVC).

TABLE IVB. Multivariate Analysis of Risk Factors for Increased Postoperative Complications in Patients Undergoing Total Gastrectomy (N = 46)

Variable	Odds-ratio	95% CI	*P*-value
Age	1.00	0.92–1.08	0.99
ASA	1.26	0.15–10.35	0.83
EBL	1.00	0.99–1.01	0.22
T-stage	0.91	0.30–2.80	0.87
N-stage	0.85	0.38–1.91	0.70
J-tube placement	0.61	0.07–5.13	0.65

TABLE IVC. Multivariate Analysis of Factors Associated With Adjuvant Therapy in Patients Undergoing Total Gastrectomy (N = 46)

Variable	Odds-ratio	95% CI	*P*-value
Age	0.98	0.92–1.04	0.49
ASA	0.20	0.02–2.07	0.18
T-stage	1.24	0.64–2.43	0.53
N-stage	1.32	0.73–2.40	0.35
J-tube placement	1.69	0.41–6.86	0.47

Although statistical significance was not reached, of those patients who actually received adjuvant therapy after total gastrectomy, 72% (n = 21) had a J-tube in place compared to 28% (n = 8) who did not.

Subtotal Versus Total Gastrectomy

Although the patients who underwent J-tube placement were evenly divided between those who underwent a subtotal (n = 34) versus total (n = 32) gastrectomy, a greater percentage of patients who underwent total gastrectomy received J-tubes compared to those undergoing a subtotal gastrectomy (70% vs. 40%). In order to exclude this finding as a potential confounding factor in our analysis of the effect of J-tube placement, a separate analysis was performed comparing the main outcomes of patients undergoing each type of procedure. There was no difference in LOS between subtotal and total gastrectomy (11.7 vs. 12.5 days, $P = 0.53$). The incidence of postoperative complications was identical between the two groups (50%), as was specifically infectious complications (26% vs. 28%, $P = 0.74$). Finally, the rate at which patients received adjuvant therapy was similar between groups (54% vs. 63%, $P = 0.29$; Table V).

DISCUSSION

The purpose of this study was to assess the value of placing J-tubes at the time of gastrectomy for gastric adenocarcinoma. Malnutrition following resection for gastric adenocarcinoma remains a serious concern which can lead to increased postoperative complications and patient morbidity [4]. J-tube placement at the time of gastrectomy offers a means by which to increase postoperative caloric intake. One potential benefit of optimizing nutritional status is to increase the rate of successful administration of adjuvant therapy after surgery. There are little data examining the actual clinical benefit of enteral J-tubes placed at the time of gastrectomy.

One might expect that the patients who are selected for J-tube placement are those who have a pre-existing poor nutritional status at the time of operation or those who are undergoing a larger gastric resection. In this study, there was no difference in the preoperative nutritional status between patients who did and did not have a J-tube placed as measured by preoperative serum albumin levels (Table IIA). BMI was also similar between the two groups. Thus, it was not the case that either severely emaciated or morbidly obese patients were concentrated in one group versus the other. J-tube placement did not seem to augment nutritional status postoperatively, as there was no measurable difference in postoperative nutritional status between the two groups, although complete postoperative albumin level data was not available. Furthermore, the patients who had a J-tube placed were evenly split between those who underwent a subtotal gastrectomy and those who underwent a total gastrectomy. There was, however, a tendency to place J-tubes more often in patients undergoing a total gastrectomy compared to a subtotal gastrectomy. Given this foreseen possibility, a subset analysis was planned at the outset of this study to assess the patients stratified by the type of operation.

TABLE V. Comparison of Patients Undergoing Subtotal Versus Total Gastrectomy

Variable	Subtotal (n = 86)	Total (n = 46)	*P*-value
LOS (days)	11.7 (2–29)[a]	12.5 (5–28)[a]	0.53
Any complication	43 (50%)	23 (50%)	1.00
Infectious complication	22 (26%)	13 (28%)	0.74
Adjuvant therapy	46 (54%)	29 (63%)	0.29

LOS, length of hospital stay.
[a]Mean (range).

In this study of 132 patients who underwent gastric resection, J-tube placement was associated with a higher incidence of postoperative complications. This finding persisted in a multivariate regression analysis as J-tube placement was associated with increased complications even when accounting for such known risk factors as increased patient age, more comorbidities as measured by ASA class, advanced tumor stage, intraoperative difficulty as measured by estimated blood loss, and a greater extent of operation, that is, total gastrectomy (Table IIB). Patients with J-tubes were also found to have higher infectious complications (36% vs. 17%, $P = 0.01$). The most common type of infectious complication was surgical site infection (n = 14) that required opening of the wound and antibiotic treatment. J-tube placement was also associated with a 2-day increased LOS that was independent of the extent of surgery.

As mentioned previously, the incentive to place a J-tube is guided by the potential of optimizing postoperative nutritional status to increase the rate of administering adjuvant therapy. The MAGIC trial clearly demonstrated the difficulty that patients have with postoperative treatment as only 42% of patients randomized to the treatment arm were able to withstand their postoperative chemotherapy [7]. Despite J-tube placement, in this study there was no difference observed in postoperative nutritional status as measured by serum albumin levels at 30, 60, and 90 days after operation, suggesting that it was not significantly impacting nutritional status. Furthermore, only a little over half of the patients who underwent J-tube placement actually received enteral nutrition through the tube at the time of hospital discharge due to limited tolerance of tube feeds. Finally, there was no significant increase in the percentage of patients with J-tubes who received adjuvant therapy (61% vs. 53%, $P = 0.38$). In a multivariate analysis, advanced age and ASA class were associated with a decreased likelihood of receiving adjuvant therapy, and J-tube placement did not seem to confer any advantage (Table IIC). These findings suggest that J-tubes should not be placed routinely in all patients undergoing gastrectomy for gastric cancer as the increased risk of perioperative complications seem to outweigh the potential benefit of improving nutritional status and increasing delivery of adjuvant therapy.

In order to assess patients separately by the operation type, a planned subgroup analysis was performed. The patients who underwent a subtotal gastrectomy with J-tube placement did experience a significantly higher rate of postoperative complications, of which many were infectious, specifically incision related, in nature. This association of increased complications with J-tube placement was also observed in a multivariate regression analysis, even when accounting for advanced tumor stage and intraoperative difficulty as measured by estimated blood loss (Table IIIB). Also, they tended to stay in the hospital for 2 days longer than their counterparts who did not have J-tubes placed. It is important to note that the patients who received a J-tube were not more preoperatively malnourished as measured serum albumin level compared to those who did not get a J-tube. Furthermore, it did not seem that J-tube placement provided any nutritional or oncologic advantage, as there was no demonstrable improvement in postoperative nutritional status as measured by serum albumin levels, and there was no difference in the rate of receiving adjuvant therapy (Table IIIC).

In a similar subset analysis for those patients undergoing total gastrectomy, placement of a J-tube did not seem to be associated with the same increased rate of complications as was observed in patients who underwent a subtotal gastrectomy (Tables IVA and IVB). Similar to the subtotal gastrectomy cohort, there was no difference in preoperative nutritional status in patients undergoing a total gastrectomy who did and did not receive a J-tube. Although nearly 70% of patients utilized their J-tube for feeding prior to

hospital discharge, there was still no demonstrable improvement in postoperative nutritional status as measured by 30-, 60-, and 90-day serum albumin levels. J-tube placement also was not associated with an increased rate of receiving adjuvant therapy (Table IVC). Despite this, it seemed that patients who underwent a total gastrectomy and received adjuvant therapy were more likely to have a J-tube in place (72% vs. 28%).

One potential confounding factor is that although the number of patients who received a J-tube was evenly split between those undergoing a subtotal versus total gastrectomy, those patients undergoing a total gastrectomy were more likely to receive a J-tube (70% vs. 40%). However, in a multivariate analysis (Table IIB), the extent of operation was not significantly associated with increased postoperative complications; only J-tube placement was associated with increased complications. Furthermore, the LOS, complications, and rate of receiving adjuvant therapy were similar between patients undergoing a subtotal versus total gastrectomy, regardless of J-tube placement. Thus, it seems that indeed J-tube placement is independently associated with increased complications with no demonstrable advantage in nutritional status and adjuvant therapy.

The main limitation of this study is its retrospective nature. It is difficult to completely account for the selection process that dictated which patients received a J-tube at the time of gastrectomy. There also may be individual surgeon bias in the decision of whether to place a J-tube. That being said, preoperative nutritional status was not different between patients as measured by their serum albumin levels, a reliable and validated measure of nutritional status [14–16]. Although J-tube utilization data was available for all patients while still in the hospital, it was difficult to retrospectively capture data regarding J-tube feeds in the outpatient arena. The limited use of J-tubes for feeding may be criticized and makes it difficult to definitively comment on the effect on postoperative nutritional status, but in reality, likely accurately reflects the clinical fact that not all patients tolerate tube feeds. Finally, the measure of postoperative nutritional status was limited to serum albumin levels in select patients. This data was not available on all patients since this laboratory value was not checked routinely in everyone. Other parameters of nutritional status such as prealbumin and transferrin levels, which may be more sensitive for detecting changes in nutritional status, were not available.

CONCLUSION

J-tube placement at the time of gastrectomy for adenocarcinoma may be associated with increased postoperative complications without any demonstrable improvement in the likelihood of receiving adjuvant therapy. Subset analysis by operation type suggests that J-tube placement during total gastrectomy may have less negative consequences and may help select patients proceed to adjuvant therapy. Routine use of J-tubes after subtotal gastrectomy may not be justified. Prospective randomized controlled studies are needed to validate these findings.

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