

Efficacy of intraoperative radiotherapy targeted to the abdominal lymph node area in patients with esophageal carcinoma

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We investigated whether intraoperative radiotherapy (IORT) during curative surgery for esophageal carcinoma is useful or not. The cases of 117 patients diagnosed with thoracoabdominal esophageal carcinoma who underwent curative surgery between 1986 and 2007 were reviewed: 72 patients received IORT (IORT group) and 45 did not (non-IORT group). Upper abdominal lymphadenectomy was performed in 115 patients (98.5%). Seventy patients (59.8%) received chemotherapy and 80 patients (68.4%) received external radiotherapy. IORT encompassed the upper abdominal lymph node area. A single-fraction dose of 20–30 Gy was delivered using high-energy electrons. Median follow-up duration for patients was 7.4 years. The 5-year overall survival rate did not significantly differ between the IORT and non-IORT groups. However, the 5-year abdominal control rate was significantly higher in the IORT group (89.2%) than in the non-IORT group (72.9%; $P=0.022$). We next focused on a patient subgroup with a primary lesion in the lower thoracic or abdominal esophagus or measuring >6 cm in length since this subgroup is probably at high risk of upper abdominal lymph node metastasis. Of the 117 patients, 75 belonged to this subgroup, and among them 45 received IORT. Both univariate and multivariate analysis revealed the survival rate was significantly higher in patients who received IORT than in those who did not ($P=0.033$ univariate; 0.026 multivariate). There were no obvious perioperative complications solely attributed to IORT. IORT for esophageal carcinoma will likely be effective for patients with a primary lesion in the lower thoracic or abdominal esophagus, or with a long lesion.

Keywords: esophageal carcinoma; intraoperative radiotherapy; abdominal controllability; overall survival; safety

INTRODUCTION

Esophageal carcinoma is one of the most difficult cancerous diseases to cure, despite the common use of multimodal therapy such as surgery, radiotherapy, and chemotherapy,

and it has a poor prognosis [1, 2]. The reason for the poor prognosis is that most patients present with advanced stage disease, with the tumor metastasizing to the lymph nodes even in the early stages of the disease [3]. It is characterized by extensive local growth, lymph node metastasis, and

distant metastasis, and its spread is greatly affected by its vertical location because the esophagus is a long organ [4].

Management of lymph node metastasis is a critical issue in treatment of esophageal carcinoma; metastasis is considered to be one of the most important prognostic factors in patients who undergo curative surgery [5–8]. According to several studies, 58–74% of patients undergoing esophagectomy for thoracic esophageal carcinoma were diagnosed histologically as having lymph nodes metastasis [9–11]. Zhang *et al.* examined the 5-year survival rate by the number of metastatic lymph nodes and found a survival rate of 59.8% in patients with no metastatic lymph nodes, compared to just 33.4% and 9.4% in those with one metastatic node and two or more metastatic nodes, respectively [12]. Esophageal carcinoma in the upper thoracic esophagus frequently metastasizes to the cervical nodes, whereas that in the lower thoracic esophagus tends to metastasize to nodes in the upper abdominal area [4, 13, 14]. Tachimori *et al.* focused on the anatomical lymphatic drainage system in patients with a primary lesion in the lower thoracic esophageal area [15] and found metastasis in the perigastric lymph node area in a high proportion (65.6%) of patients with a pathological T2–4 tumor and in 39.5% of patients with a pathological T1 tumor. These findings suggest that the risk of metastasis to the perigastric lymph nodes, as well as to lower mediastinal lymph nodes, should be taken into consideration. Even after curative treatment for esophageal cancer, recurrence at the abdominal lymph node is still frequently observed and remains a critical problem [16–18]. Moreover, most patients with esophageal carcinoma have squamous cell carcinoma pathologically, considered to be more radio-sensitive than adenocarcinoma in Japan [19].

Intraoperative radiotherapy (IORT) was developed by Abe *et al.* in 1964 and used mainly for the treatment of carcinoma of the stomach and pancreas [20]. This treatment modality was introduced into the US and other countries and applied to a variety of malignant tumors [21]. IORT delivers high-dose radiation directly to targeted tumors and potential tumor sites, while also sparing the surrounding important organs if they are manually displaced from the radiation field. IORT for advanced cervical node metastasis has afforded good local disease control with acceptable levels of toxicity [22]. The efficacy of IORT on the tumor bed in the upper abdominal area, in addition to curative surgery, has also been demonstrated in patients with advanced gastric cancer [23]. However, the effectiveness of IORT for esophageal carcinoma has been poorly studied thus far: in 1993, Arimoto *et al.* reported successful prevention of mediastinal lymph node metastasis by IORT targeted at the upper mediastinum [24], while in 1999 Murakami *et al.* showed that IORT to the upper abdominal lymph node area was useful for esophageal carcinoma [25].

We started performing IORT at Tenri Hospital in 1992 to improve the control rate in the upper abdominal lymph

node area in an effort to improve overall survival rates of patients with esophageal carcinoma. Our concern was that microscopic residual tumor in the upper abdominal area might cause abdominal recurrence, though it was performed with curative resection. Therefore, we inferred that IORT to the upper abdominal area in combination with local curative resection would have a good effect on treatment outcome. The purpose of this study was to evaluate the effectiveness of our treatment strategy for esophageal carcinoma, especially focusing on the contribution of IORT to overall survival and abdominal regional controllability.

MATERIALS AND METHODS

Patients

Cases were reviewed of patients diagnosed with thoracoabdominal esophageal carcinoma who underwent curative surgery at Tenri Hospital between July 1986 and July 2007. Cases of pathological Stage IVB disease, according to the International Union Against Cancer (UICC) 2002 staging system [26], were excluded. Similarly, cases of unsuccessful curative resection were excluded. The remaining 117 cases were examined in this study.

Outcomes were retrospectively compared between the group that received curative surgery with IORT targeted to the upper abdominal area (IORT group, $n = 72$) and the group that received curative surgery without IORT (non-IORT group, $n = 45$). Reasons why IORT was not performed in these 45 cases included timing of the treatment (IORT was introduced in April 1992), patient refusal, equipment problems, likelihood of a prolonged surgical procedure indicated in the preoperative assessment conference (e.g. involving extensive dissection of the pharynx, larynx, and stomach), and cancellation of IORT due to systemic deterioration during surgery attributed to increased bleeding, unstable vital signs, and unexpected delays during surgical procedures.

Table 1 shows the patient characteristics in each group. Pathological stage was determined according to the UICC 2002 staging system. None of the characteristics shown in Table 1, including patient medical conditions, differed significantly between the two patient groups.

Treatments

All patients received curative surgery. Subtotal esophagectomy was performed in most patients, while middle-lower thoracic and abdominal esophagectomy was performed when small primary lesions were present in the lower thoracic esophagus, when primary lesions were present in the abdominal esophagus or when gastrectomy was performed at the same time. Upper abdominal lymphadenectomy was performed in 115 patients (72 in the IORT group, 43 in the non-IORT group), mediastinal lymphadenectomy in

Table 1. Patient characteristics

	IORT group ^a	Non-IORT group	Total	<i>P</i> -value ^b
No. of cases	72	45	117	
Age, years	44–78	44–78	44–78	0.66
(median)	(60.5)	(63.0)	(62.0)	
Male	60	41	101	0.36
Female	12	4	16	
Performance status				0.44
0	49	23	72	
1	19	18	37	
2	3	4	7	
3	1	0	1	
4	0	0	0	
Primary site				0.73
upper thoracic esophagus	5	4	9	
middle thoracic esophagus	32	17	49	
lower thoracic esophagus	35	22	57	
abdominal esophagus	0	2	2	
Tumor length				0.89
>6 cm	29	19	48	
≤6 cm	42	26	68	
(no description)	(1)	(0)	(1)	
Histology				0.06
squamous cell carcinoma	71	40	111	
adenocarcinoma	1	5	6	
Pathological stage				0.44
0 and PCR ^c	4	1	5	
I	8	7	15	
IIA	22	10	32	
IIB	19	9	28	
III	12	16	28	
IVA	7	2	9	
Pathological T stage				0.99
Is and PCR	4	1	5	
1	18	10	28	
2	17	10	27	
3	31	22	53	
4	2	2	4	
Pathological N stage				0.33
0	35	26	61	
1	37	19	56	

Continued

Table 1. *Continued*

	IORT group ^a	Non-IORT group	Total	<i>P</i> -value ^b
Pathological upper abdominal lymph node metastasis				0.86
positive	23	15	38	
negative	49	30	79	
High risk subgroup; lesion localized in lower thoracic or abdominal esophagus or >6 cm in length				0.65
cases who belong to this subgroup ^d	45	30	75	
cases who do not belong to this subgroup	27	15	42	

^aintraoperative radiotherapy, ^b*P*-value indicates statistical differences between IORT and non-IORT groups, ^cpathological complete response after preoperative chemotherapy and radiotherapy, ^dlesion localized in the lower thoracic or abdominal esophagus or >6 cm in length is used for subgroup analysis in Table 2, as a high risk group.

113 patients (71 and 42, respectively), and cervical lymphadenectomy in 94 patients (65 and 29, respectively).

Of the 117 patients, 80 (68%) received external radiotherapy and 70 patients (60%) received chemotherapy. Details of chemotherapy and external radiotherapy in the IORT group and the non-IORT group are shown in Table 2. The radiation dose delivered during preoperative radiotherapy was 44 Gy (33–56 Gy), while that in postoperative radiotherapy was 50 Gy (30–60.4 Gy). However, less than 40 Gy was unavoidably delivered to 2 patients during preoperative radiotherapy and 3 patients during postoperative radiotherapy, while more than 55 Gy was delivered in 4 patients in preoperative and postoperative radiotherapy. In this study, external radiotherapy was provided as adjunctive therapy. Preoperative radiotherapy was performed to increase complete resectability in the subsequent surgery, while postoperative radiotherapy was performed to prevent recurrence. The target volume of the external radiotherapy was localized to the various sites of primary lesions. Therefore, only 5 patients with multiple or large abdominal lymph node metastases, or the primary lesion located in the abdominal esophagus, received external radiotherapy to the upper abdominal area. Regarding our concern about normal tissue tolerance, no patient in the IORT group received external radiotherapy to the upper abdominal area.

Intraoperative radiotherapy

IORT was performed immediately after the surgical procedures in the chest area were completed and the esophagus was resected. In Tenri Hospital, the linear accelerator used for IORT was also used for radiotherapy for outpatients. With our patients, IORT was performed only on Mondays so that patients could be treated immediately after

Table 2. Details of external radiotherapy and chemotherapy in the IORT group and the non-IORT group

	IORT group (<i>n</i> = 72)	non-IORT group (<i>n</i> = 45)
External radiotherapy	57 (79%)	23 (51%)
Upper abdominal area	0 (0%)	5 (11%)
Mediastinal area	53 (74%)	20 (44%)
Cervical area	22 (31%)	10 (22%)
Preoperative	32 (44%)	7 (16%)
Postoperative	10 (14%)	14 (31%)
Both	15 (21%)	2 (4%)
Chemotherapy	50 (69%)	20 (44%)
Preoperative	35 (48%)	9 (20%)
Postoperative	2 (3%)	9 (20%)
Both	13 (18%)	2 (4%)
Cisplatin and 5-fluorouracil	48 (66%)	17 (38%)
Nedaplatin and 5-fluorouracil	2 (3%)	0 (0%)
Cisplatin	0 (0%)	1 (2%)
S-1	0 (0%)	2 (4%)

ultraviolet sterilization over the weekend. While patients were moved under general anesthesia between the operating room on the seventh floor and the radiation unit on the first basement floor, surgical incision sites were temporarily closed and an accompanying anesthesiologist continuously managed the artificial respirator. Before leaving the operating room, surgeons and radiation oncologists simulated

preparation of the determined radiation fields. A circular cone with a diameter of 5–6 cm and a bevel angle of 0 or 15 degrees was usually used. IORT encompassed the upper abdominal lymph node area, including the right and left cardia, left gastric artery, celiac artery, and upper para-aortic area. Maximum efforts were made to spare as much normal tissue as possible. The liver was mobilized superiorly and the stomach and the small intestine were mobilized inferiorly with the cone. However, the upper one-third of the head and body of the pancreas were exposed to radiation to the celiac axis. The absorbed doses in several planes or along various directions were measured and the beam profiles were plotted using a water phantom. A single-fraction dose of 20–30 (median 23 Gy) using high-energy electrons (9–12 MeV) was delivered. The energy of therapeutic electrons (9–12 MeV) was determined, depending on the depth, so as to cover the microscopic residual tumors.

Statistical analysis

The Mann-Whitney U-test and the chi-squared test were used to determine differences between the patient groups in the continuous numeric and nominal variables, respectively. Overall survival rates and regional control rates of the abdominal lymphatic system were estimated by the Kaplan-Meier method and compared using the log-rank test, with a *P*-value of less than 0.05 considered statistically significant. Multivariate analysis was performed using a proportional hazard model.

RESULTS

Median follow-up duration was 7.4 years (range, 0.1–16.6 years). Seven patients (6.0% of the total: 6 in the IORT group, 1 in the non-IORT group) were lost to follow-up before the end of the third year after treatment, which was determined as the final follow-up point. In addition, 9 patients (7.7% of the total: 7 in the IORT group, 2 in the non-IORT group) were lost to follow-up before the end of the fifth year after treatment.

The recurrence rate was 41.7% (30 patients) in the IORT group and 57.8% (26 patients) in the non-IORT group. The incidence of first recurrence in the upper abdominal lymph node area was lower in the IORT group (2.8%, 2 patients) than in the non-IORT group (13.3%, 6 patients). The incidence rates of other locoregional recurrence (including local recurrence and recurrence in the cervical lymph node area or mediastinal lymph node area) were not much different between the IORT group (18.1%, 13 patients) and the non-IORT group (20.0%, 9 patients). In the same way, the incidence rate of recurrence in the distant area was not much different between the IORT group (20.8%, 15 patients) and the non-IORT group (24.4%, 11 patients). When the control rates in the abdominal lymph node area

(combining the upper abdominal lymph node area and the para-aortic lymph node area) were compared, both 3- and 5-year abdominal control rates were significantly higher in the IORT group than in the non-IORT group: 3- and 5-year control rates were 92.3% and 89.2%, respectively, in the IORT group, compared to 76.6% and 72.9%, respectively, in the non-IORT group (*P* = 0.022; Fig. 1).

Next, we compared the survival rates between the two patient groups. As shown in Figure 2, the respective 3- and 5-year overall survival rates were 57.6% and 52.8% in the IORT group and 48.8% and 34.7% in the non-IORT group, a non-significant difference (*P* = 0.17). We then grouped patients by pathological stage to perform subgroup analysis. Among patients with a pathological complete response (pCR) and pathological Stage 0–I tumor, the 5-year survival rate did not significantly differ between the IORT group (74.1%) and the non-IORT group (37.5%; *P* = 0.18). Similarly, there were no statistically significant differences

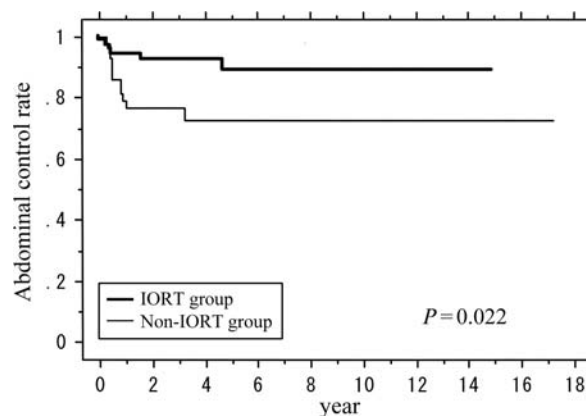


Fig. 1. Kaplan-Meier analysis of abdominal lymph node control rate in the intraoperative radiotherapy (IORT) group (*n* = 72) and non-IORT group (*n* = 45).

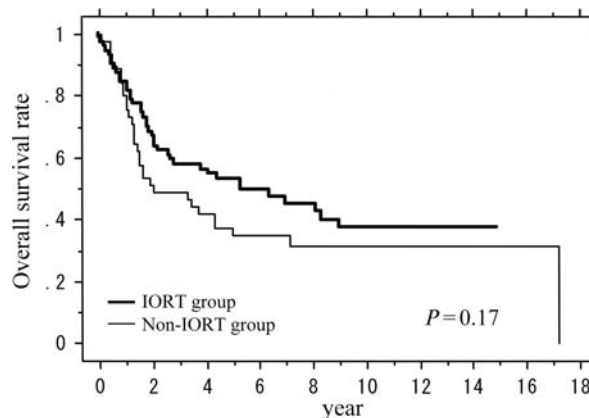


Fig. 2. Kaplan-Meier analysis of overall survival rate in IORT group (*n* = 72) and non-IORT group (*n* = 45).

in the survival rates between the two groups among pathological Stage II patients (56.1% in the IORT group, 54.2% in the non-IORT group; $P=0.79$) or among pathological Stage III–IVA patients (33.3% in the IORT group, 11.8% in the non-IORT group; $P=0.19$). We examined treatment outcomes in both groups among patients with and without lymph node metastases. The 5-year survival rate was 34.1% in the IORT group and 26.9% in the non-IORT group ($P=0.65$) in patients with lymph node metastases, and it was 77.2% in the IORT group and 46.3% in the non-IORT group ($P=0.088$) in patients without lymph node metastases. The differences in 5-year survival rates between the IORT and non-IORT groups were not significant, regardless of lymph node metastases. We also examined the contribution to the survival rate of using external radiotherapy to the upper abdominal area, as well as IORT. The 5-year survival rate was 0% in the group of 5 patients who received external radiotherapy to the upper abdominal area and 47.6% in the group of 112 patients who did not ($P=0.0019$).

Furthermore, we assessed a subgroup of patients with the primary lesion located in the lower thoracic or abdominal part of the esophagus or measuring >6 cm in length, as patients in this subgroup tend to have lymph node metastasis in the upper abdominal area and thus are more likely to benefit from IORT targeted to this area. Among

the 117 patients examined in this study, 75 patients belonged to this subgroup. Table 3 shows the number of patients in this subgroup who did or did not receive IORT, chemotherapy, and external radiotherapy. Univariate analysis examining the factors potentially associated with the overall survival rate (i.e. IORT, chemotherapy, external radiotherapy, age, and performance status (PS)) revealed that the 5-year overall survival rate was significantly higher in patients with PS 0 than in those with PS 1–4 ($P=0.0029$). The 5-year overall survival rate was significantly different between patients who received IORT and those who did not receive it in this subgroup (61.7% versus 32.1%, respectively; $P=0.033$; Fig. 3, Table 3). On the other hand, chemotherapy, external radiotherapy and patient age did not appear to influence the overall survival rate. We performed multivariate analysis using a proportional hazards model. The factors used were IORT, chemotherapy, external irradiation, age and performance status. In multivariate analysis, the 5-year overall survival rate was also significantly higher in those with PS 0 than in those with PS 1–4 ($P=0.0019$) and in those who received IORT than in those who did not ($P=0.026$; Table 3). In addition, in this subgroup of patients, the 5-year abdominal control rate was 88.8% in the IORT group and 62.7% in the non-IORT group. The difference between the two groups was significant ($P=0.011$).

Table 3. Results of univariate analysis and multivariate analysis of factors influencing survival rate in 75 patients with a primary lesion in the lower thoracic or abdominal part of the esophagus or with a primary lesion >6 cm in length

Characteristics	Univariate analysis		Cox's multivariate regression analysis	
	5-year survival rate	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
IORT		0.033	0.47 (0.25–0.92)	0.026
with IORT (<i>n</i> = 45)	61.7%			
without IORT (<i>n</i> = 30)	32.1%			
Chemotherapy		0.73	0.54 (0.27–1.01)	0.085
with chemotherapy (<i>n</i> = 40)	51.7%			
without chemotherapy (<i>n</i> = 35)	46.7%			
External radiotherapy		0.82	1.29 (0.65–2.58)	0.47
with external radiotherapy (<i>n</i> = 43)	52.8%			
without external radiotherapy (<i>n</i> = 32)	44.5%			
Age		0.26	1.58 (0.84–2.99)	0.16
≤60 years old (<i>n</i> = 30)	55.0%			
60 years old (<i>n</i> = 45)	45.4%			
Performance status		0.0029	0.36 (0.19–0.69)	0.0019
0 (<i>n</i> = 44)	63.3%			
1–4 (<i>n</i> = 31)	1.7%			

HR = hazard ratio, CI = 95% confidence interval.

In regard to perioperative complications (Table 4), the number of cases was higher, although not significantly so, in the IORT group compared to the non-IORT group (35 (48.6%) versus 22 (48.9%) of cases, respectively; $P=0.98$). Typical complications included wound infection, pneumonia, anastomotic leaks and anastomotic stenosis, but incidence rates of these complications were not significantly different between the IORT and non-IORT groups. None of the 117 patients showed adverse events directly attributable to IORT, such as liver function disorder, pancreas function disorder or pancreatic necrosis.

DISCUSSION

Our approach to treating esophageal carcinoma, incorporating IORT immediately postoperatively, is thought to be a unique one. Although the efficacy of IORT, which delivers

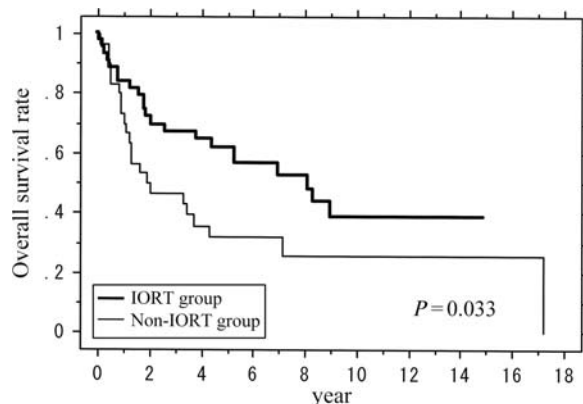


Fig. 3. Kaplan-Meier analysis of overall survival rate in the IORT group ($n=45$) and non-IORT group ($n=30$) within the subgroup of patients whose primary lesion was located in the lower thoracic or abdominal part of the esophagus or measured >6 cm in length.

high-dose radiation directly to sites at a high risk of recurrence during curative surgery, has been theoretically accepted, detailed treatment outcomes have rarely been reported. We first examined the validity of IORT in the control of the abdominal lymphatic system, finding that the rate of first recurrence in the upper abdominal lymph node area was lower in the IORT group (2.8%) than in the non-IORT group (13.3%), suggesting better control in the former group. The control rate in the abdominal area was significantly higher in the IORT group than in the non-IORT group. On the other hand, the recurrence rates in the cervical area and mediastinal area were comparable between the two groups. Thus, it appears that performing IORT contributes to local control in the upper abdominal area. The overall survival rates, on the other hand, were not significantly different between the IORT and non-IORT groups, suggesting that the overall survival rate in patients with esophageal carcinoma cannot be effectively improved solely by adding IORT targeted to the upper abdominal area. This may be explained by the fact that the outcome of esophageal carcinoma treatment is influenced by complex factors involving surgical protocol, curability of surgical treatment, chemotherapy regimen and schedule, radiation field and dose used in external radiotherapy, and accuracy of preoperative diagnostic imaging.

We considered that external radiotherapy, as well as IORT, could influence disease control in the upper abdominal area. However, comparative analysis showed poorer treatment outcome in patients who received external radiotherapy than in those who did not. This poor outcome can be explained by the fact that external radiotherapy was performed mostly in patients at high risk of disease recurrence after surgery. The outcome may also have been affected by the small sample size used. Thus, our results remain inconclusive with regard to the effect of external radiotherapy targeting the upper abdominal area on treatment outcome.

Akiyama *et al.* demonstrated that the 5-year overall survival rate in patients with lower thoracic esophageal

Table 4. Complications

	IORT group $n = 72$	Non-IORT group $n = 45$	Total $n = 117$	<i>P</i> -value
No. of cases	35 (48.6%)	22 (48.9%)	57	0.13
Wound infection and abscess formation	5 (6.9%)	3 (6.7%)	8	0.75
Pneumonia, pleural effusion, and chylothorax	10 (13.8%)	7 (15.6%)	17	0.98
Anastomotic leak in the neck	9 (12.5%)	3 (6.7%)	12	0.48
Anastomotic leak in the upper abdomen	1 (1.4%)	0 (0%)	1	0.81
Anastomotic stenosis	6 (8.3%)	6 (13.3%)	12	0.58
Gastric necrosis	0 (0%)	1 (2.2%)	1	0.81
Recurrent nerve paralysis	6 (8.3%)	5 (11.1%)	11	0.86

carcinoma was 48.5% without abdominal lymph node metastasis and only 17.9% with it, and suggested that control in the abdominal area was an important factor for good outcome [16]. Also, interestingly, Eloubeidi *et al.* found that the survival rate was higher when tumor length was shorter, suggesting that tumor length is a prognostic factor and thus should be included in the factors determining TNM classification [27]. On the basis of these previous findings, we further examined a subgroup of patients whose primary lesions were located in the lower thoracic or abdominal part of the esophagus, or measured >6 cm in length (6cm is equivalent to about 1/3 or 1/4 of the full length of the thoracoabdominal esophagus): patients in this subgroup are considered to be at high risk for abdominal lymph node metastasis. Of our 117 patients with esophageal carcinoma, 75 (64.1%) belonged to this subgroup. Both univariate and multivariate analysis revealed that, within this subgroup, the survival rates were high in patients with PS 0 and in those who received IORT. This suggests that the control of the abdominal lymphatic system brought by performing IORT contributes to improving survival rate in this subgroup. In other words, lymphadenectomy alone is not sufficient in this subgroup, and this suggests that microscopic residual tumors are present in the treated area in these patients. We were concerned about recurrence in the abdominal area, and administered IORT to the upper abdominal area in addition to lymphadenectomy in high-risk patients for control of microscopic residual tumors. It is possible that this led to the improvement of therapeutic outcomes.

Our results agree with the study by Matsubara *et al.* in which they reported high incidence rates of metastasis in the para-aortic lymph node area, liver, and peritoneum in the patients with recurrence in the upper abdominal lymph node area [28]. Wu *et al.* also reported that, among patients with thoracic esophageal carcinoma, the survival rate was significantly poorer in those with perigastric lymph node metastasis than in those without it, suggesting the importance of control in this area [29]. Thus, it would seem worthwhile to offer IORT to patients with the above recurrence and metastasis profiles.

Lymph node recurrence is the key determinant of disease prognosis. Lanschot *et al.* studied the recurrence pattern after esophageal surgery in detail, finding that local control was crucial in improving the survival rate in one third of patients [30]. Further, Morita *et al.* assessed lymph node metastasis and hematogenous metastasis, and concluded that focus should be put on local control, as well as systemic management, in the treatment for esophageal carcinoma [31]. Taken together, both systemic management and the control of local lesions are essential in the treatment of esophageal carcinoma, and IORT can play an important role in local control. Esophageal carcinoma spreads via

multiple routes, and local control and preventing tumor spread via lymphogenous and hematogenous routes should be carefully considered.

We did not find complications directly attributable to IORT. Also, despite our initial concerns, IORT itself and the accompanying longer operation times and longer duration of anesthesia did not increase the incidence of perioperative complications. A temporary elevation in the serum amylase level was reported in patients who underwent IORT targeted to the stomach, probably due to radiation to the pancreas [32], but this was absent in all patients in the present study. Thus, we believe that IORT is safe to perform during surgery for esophageal carcinoma.

In our study, external radiotherapy was adjunct to curative surgery, and postoperative radiotherapy was selectively performed according to surgical and histopathological findings. The significance of postoperative radiotherapy has been investigated in previous studies, wherein no improvement in survival outcome was observed [33, 34]. On the contrary, preoperative radiotherapy appears important to increase complete resectability. In Western countries, it has been reported that chemoradiotherapy, before curative surgery, significantly improved treatment outcomes compared with curative surgery alone in patients with resectable cancer [35]. However, in a separate report, preoperative chemoradiotherapy was shown to improve treatment outcome, but it also significantly increased postoperative deaths due to perioperative complications [36]. In our study, the incidence of perioperative complications in the IORT group was not significantly different to that in the non-IORT group, indicating the therapeutic benefit of IORT, a possible improvement in treatment outcome without compromising the safety of the treatment.

This study has certain limitations. First, the effects of selection bias are not negligible as this is a retrospective study. Second, the treatment protocol was not uniform among patients; for example, the use of chemotherapy and/or external radiotherapy was not in common, and thus the outcome of treatment in individual patients was influenced by the modalities used. The standardization of regimens for chemotherapy and external radiotherapy (field and dose of radiation) is necessary in the future.

CONCLUSION

In conclusion, albeit with some limitations, IORT targeted to the upper abdominal lymph node area is effective in obtaining good local control. It is also beneficial for treating patients with lower thoracic or abdominal esophageal carcinoma and those with a long primary lesion, as it can improve survival rates in these patients. IORT shows promise as an effective treatment option for such patients.

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REFERENCES

- Shimada Y, Imamura M, Sato F *et al.* Indications for abdominal para-aortic lymph node dissection in patients with esophageal squamous cell carcinoma. *Surgery* 2002;**132**: 93–9.
- Orringer MB. Transhiatal esophagectomy without thoracotomy for carcinoma of the thoracic esophagus. *Ann Surg* 1984;**200**:282–8.
- Igaki H, Kato H, Tachimori Y *et al.* Prognostic evaluation for squamous cell carcinomas of the lower thoracic esophagus treated with three-field lymph node dissection. *Eur J Cardiothorac Surg* 2001;**19**:887–93.
- Doki Y, Ishikawa O, Takachi K *et al.* Association of the primary tumor location with the site of tumor recurrence after curative resection of thoracic esophageal carcinoma. *World J Surg* 2005;**29**:700–7.
- Kang CH, Kim YT, Jeon SH *et al.* Lymphadenectomy extent is closely related to long-term survival in esophageal cancer. *Eur J Cardiothorac Surg* 2007;**31**:154–60.
- Lerut T. Esophageal surgery at the end of the millennium. *J Thorac Cardiovasc Surg* 1998;**116**:1–20.
- Clark GW, Peters JH, Ireland AP *et al.* Nodal metastasis and sites of recurrence after en bloc esophagectomy for adenocarcinoma. *Ann Thorac Surg* 1994;**58**:646–53.
- Hölscher AH, Bollschweiler E, Bumm R *et al.* Prognostic factors of resected adenocarcinoma of the esophagus. *Surgery* 1995;**118**:845–55.
- Ide H, Nakamura T, Hayashi K *et al.* Esophageal squamous cell carcinoma: pathology and prognosis. *World J Surg* 1994;**18**:321–30.
- Kato H, Watanabe H, Tachimori Y *et al.* Evaluation of neck lymph node dissection for thoracic esophageal carcinoma. *Ann Thorac Surg* 1991;**51**:931–5.
- Isono K, Sato H, Nakayama K. Results of a nationwide study on the three-field lymph node dissection of esophageal cancer. *Oncology* 1991;**48**:411–20.
- Zhang HL, Chen LQ, Liu RL *et al.* The number of lymph node metastases influences survival and International Union Against Cancer tumor-node-metastasis classification for esophageal squamous cell carcinoma. *Dis Esophagus* 2010;**23**:53–8.
- Fujita H, Kakegawa T, Yamana H *et al.* Lymph node metastasis and recurrence in patients with a carcinoma of the thoracic esophagus who underwent three-field dissection. *World J Surg* 1994;**18**:266–72.
- Doki Y, Ishikawa O, Kabuto T *et al.* Possible indication for surgical treatment of squamous cell carcinomas of the esophagus that involve the stomach. *Surgery* 2003;**133**: 479–85.
- Tachimori Y, Nagai Y, Kanamori N *et al.* Pattern of lymph node metastases of esophageal squamous cell carcinoma based on the anatomical lymphatic drainage system. *Dis Esophagus* 2011;**24**:33–8.
- Akiyama H, Tsurumaru M, Udagawa H *et al.* Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg* 1994;**220**:364–73.
- Bhansali MS, Fujita H, Kakegawa T *et al.* Pattern of recurrence after extended radical esophagectomy with three-field lymph node dissection for squamous cell carcinoma in the thoracic esophagus. *World J Surg* 1997;**21**:275–81.
- Nakagawa S, Kanda T, Kosugi S *et al.* Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. *J Am Coll Surg* 2004;**198**:205–11.
- Shirai K, Tamaki Y, Kitamoto Y *et al.* Comparison of chemoradiotherapy with radiotherapy alone in patients with esophageal adenocarcinoma. *J Radiat Res* 2011;**52**:264–9.
- Abe M, Fukuda M, Yamano K *et al.* Intra-operative irradiation in abdominal and cerebral tumours. *Acta Radiol Ther Phys Biol* 1971;**10**:408–16.
- Willett CG, Czito BG, Tyler DS. Intraoperative radiation therapy. *J Clin Oncol* 2007;**25**:971–7.
- Zeiden YH, Yeh A, Weed D *et al.* Intraoperative radiation therapy for advanced cervical metastasis: a single institution experience. *Radiat Oncol* 2011;**6**:72.
- Abe M, Nishimura Y, Shibamoto Y. Intraoperative radiation therapy for gastric cancer. *World J Surg* 1995;**19**:554–7.
- Arimoto T, Takamura A, Tomita M *et al.* Intraoperative radiotherapy for esophageal carcinoma – significance of IORT dose for the incidence of fatal tracheal complication. *Int J Radiat Oncol Biol Phys* 1993;**27**: 1063–7.
- Murakami M, Kuroda Y, Nakajima T *et al.* Intraoperative radiotherapy for the abdominal lymphatic system in patients with esophageal carcinoma. *Dis Esophagus* 1999;**12**:270–5.
- Sobin LH, Wittekind Ch (eds), International Union Against Cancer (UICC): TNM Classification of malignant tumors, 6th edn. New York: Wiley-Blackwell, 2002.
- Eloubeidi MA, Desmond R, Arguedas MR *et al.* Prognostic factors for the survival of patients with esophageal carcinoma in the U.S.: the importance of tumor length and lymph node status. *Cancer* 2002;**95**:1434–43.
- Matsubara T, Ueda M, Takahashi T *et al.* Localization of recurrent disease after extended lymph node dissection for carcinoma of the thoracic esophagus. *J Am Coll Surg* 1996;**182**:340–6.
- Wu ZY, Yu JC, Xu LY *et al.* Prognostic significance of perigastric lymph nodes metastases on survival in patients with thoracic esophageal cancer. *Dis Esophagus* 2010;**23**: 40–5.
- van Lanschot JJ, Tilanus HW, Voormolen MH *et al.* Recurrence pattern of oesophageal carcinoma after limited resection does not support wide local excision with extensive lymph node dissection. *Br J Surg* 1994;**81**:1320–3.

31. Morita M, Kuwano H, Ohno S *et al*. Characteristics and sequence of the recurrent patterns after curative esophagectomy for squamous cell carcinoma. *Surgery* 1994;**116**:1–7.
32. Abe M, Takahashi M. Intraoperative radiotherapy: the Japanese experience. *Int J Radiat Oncol Biol Phys* 1981;**7**:863–8.
33. Ténrière P, Hay JM, Fingerhut A *et al*. Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower esophagus as shown by a multicenter controlled trial. French University Association for Surgical Research. *Surg Gynecol Obstet* 1991;**173**:123–30.
34. Fok M, Sham JS, Choy D *et al*. Postoperative radiotherapy for carcinoma of the esophagus: a prospective, randomized controlled study. *Surgery* 1993;**113**:138–47.
35. Burmeister BH, Smithers BM, Gebski V *et al*. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled Phase III trial. *Lancet Oncol* 2005;**6**:659–68.
36. Bosset JF, Gignoux M, Triboulet JP *et al*. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1995;**337**:161–7.