lowing DP continues to be a clinically relevant problem because complications arising from PF prolong postoperative hospital stay and increase the utilization of healthcare resources (7). According to recent reports, the mortality rate associated with DP is less than 5% although the morbidity rate remains high and ranges from 21.2% to 65% (1,7,8-13). PF, the most common postoperative complication after DP, occurs in 11.6% to 60% of cases (1,11). Although several surgical techniques and instruments have been devised for preventing PF following DP, correlations between surgical management and PF are still controversial (2,11,12-17,22).

In our series, we found no significant impact of surgical management on subsequent development of PF as has been reported in the literature (2,12,16,17). In terms of other complications, DGE and intra-abdominal abscess are clinically important complications. In our series, 15 patients developed DGE and all except 1 developed PF concomitantly. This suggests that PF may be a cause of DGE as a previous study has pointed to a possible association with PD (5).

We found no cases of intra-abdominal abscess or fluid collection in our study. Theoretically, there is almost no chance of infection during DP if combined bowel resection is not required. Moreover, we checked the drain cultures in 29 consecutive cases from April 2008 (provided the drain was persistent). Of these cases, 8 were drain-culture positive and all except 1 became culture positive after the 10th postoperative day (range, 3-19 days), which is longer than the median persistent drainage period. The culture results showed that all bacteria were indigenous skin flora. This suggests that intra-abdominal abscess and fluid collection may occur when the drain is not removed within 10 days. Infection is suspected to arise due to retrograde spread from the skin. Therefore, when intra-abdominal fluid was identified, we recognized the case as Grade B PF. We believe that almost all complications after DP develop due to PF. In our series, only 3 complications developed that were not associated with PF: 1 was a gastric wall perforation and the other 2 were chylous ascites.

In our series of patients, the inclusion of a closed active drain tended to reduce the persistent drainage period and significantly shorten the postoperative stay. We suspect that the closed active drain prevents the leakage of pancreatic juice from spreading into the intra-abdominal space, thus preventing retrograde infection. This may be because the drain canal is introduced earlier than is the case for an open drain, as has been described by previous authors (19-21). Given this along with previous authors' insistence of such an effect in the literature, management after PF becomes more important.

In conclusion, a closed active drain provides excellent drainage and contributes to the formation of a drain canal that helps to localize and control PF. Utilization of an LS and a closed active drain significantly shortens the postoperative hospital stay, and may thus contribute to decreased utilization of health care resources compared with other strategies.

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ORIGINAL ARTICLE

Borderline resectable pancreatic cancer: rationale for multidisciplinary treatment

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Abstract
Background Borderline resectable pancreatic cancer (BRPC) appears to be most frequently related to a positive surgical margin and has a poor prognosis after resection. However, few reports are available on differences in tumor characteristics and prognoses among resectable pancreatic cancer (PC), BRPC, and unresectable PC.
Methods Records of 133 patients resected for pancreatic ductal adenocarcinoma and 185 patients treated as locally advanced PC (LAPC) were reviewed.
Results Twenty-four patients who initially underwent resection (BRPC-s) and 10 patients who were initially treated as LAPC (BRPC-n) met the criteria for BRPC. Prognosis of BRPC was significantly better than that of unresectable PC, but was significantly worse than that of resectable PC. BRPC-s showed more frequent nerve plexus invasion ($P < 0.01$), portal vein invasion ($P < 0.01$), and loco-regional recurrence ($P = 0.03$) than resectable PC. The positive surgical margin rate was not significantly higher in BRPC-s (29%) than in resectable PC (19%) ($P = 0.41$).
Conclusions BRPC had a poorer prognosis with more local failure than resectable PC although prognosis of BRPC was significantly better than that of unresectable PC. Considering the tumor and treatment characteristics, multidisciplinary treatment including resection is required for BRPC.

Keywords Pancreatic cancer · Resection · Borderline resectable pancreatic cancer

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Introduction

Borderline resectable pancreatic cancer (BRPC) is a newly proposed category that is now being established [1–4]. BRPC tumors can be understood radiologically and technically as an intermediate stage between resectable tumor and locally advanced tumor. These tumors are often treated as resectable in some specialized centers, but are more likely to be removed with positive surgical margins, with positive margins generally being predictive of decreased survival [5, 6]. Multidisciplinary treatment for BRPC aiming to improve surgical resectability and prognosis is thought to be a promising strategy [7]. The surgical oncology group of the MD Anderson Cancer Center proposed neoadjuvant chemotherapy and chemoradiation for BRPC patients, and they reported favorable outcomes, with a low positive surgical margin rate and relatively long survival after the combined modality treatment [1, 2]. In the report of the AHPBA/SSO/SSAT Consensus Conference, it was recommended that BRPC patients should be studied separately from those with resectable PC or unresectable PC [7].

However, little information is available on the differences in patient demographics and surgical results,

including prognosis and positive surgical margin rate, between resectable PC and BRPC that might support a rationale for selective neoadjuvant therapy for BRPC patients. Furthermore, prognosis of BRPC patients initially treated with nonsurgical treatment such as chemotherapy or chemoradiotherapy has not been well documented.

The objective of this paper was to investigate clinicopathological factors and prognosis in patients with resected BRPC and to compare the above factors between patients with resected BRPC and those with resectable PC. We also compared outcomes between BRPC and unresectable PC to assess prognostic significance of surgical resectability in PC patients initially treated with nonsurgical treatment for local development of the tumor.

Methods

Definition of BRPC

BRPC was defined in this study according to the criteria for resectability status in the "NCCN Practice Guidelines in Oncology" [4]. Namely, the criteria for BRPC were as follows: (1) severe superior mesenteric vein (SMV)/portal impingement; (2) <180° tumor abutment on the superior mesenteric artery (SMA); (3) abutment or encasement of the hepatic artery, if reconstructible; and (4) SMV occlusion, if of a short segment, and reconstructible. In this study, in terms of SMV/portal impingement, only patients with bilateral SMV/portal impingement were included.

Patient population

A total of 133 patients who had undergone surgical resection for pancreatic ductal adenocarcinoma at the National Cancer Center Hospital East between January 2002 and December 2008 were examined retrospectively. No patients received neoadjuvant chemotherapy or chemoradiation. According to staging by multidetector-row computed tomography (MDCT) findings, 24 patients met the criteria for BRPC, and the remaining 109 patients had resectable pancreatic cancer. The 24 BRPC patients who were initially treated with resection were classified as BRPC-s.

In order to find BRPC patients who had been initially treated with nonsurgical therapy, resectability status of a total of 185 patients who were treated as locally advanced pancreatic cancer (LAPC) between January 2002 and December 2008 was examined. According to staging by MDCT findings, 10 patients met the criteria for BRPC, and the remaining 175 patients had unresectable pancreatic cancer. The 10 BRPC patients who were initially treated with nonsurgical therapy were classified as BRPC-n. For treatment of the 10 BRPC-n patients, chemotherapy was performed in 7 and concurrent or sequential chemoradiotherapy in 3. For treatment of the 175 unresectable PC patients, chemotherapy was performed in 120 patients, radiotherapy in 2, and concurrent or sequential chemoradiotherapy in 53. After initial therapy, surgical resection was performed in 2 patients out of the 10 BRPC-n patients, and 3 out of the 175 unresectable patients.

All patients had a confirmed pathological diagnosis as pancreatic ductal adenocarcinoma.

Operative procedure

Patients with ductal adenocarcinoma of the head of the pancreas typically underwent subtotal stomach-preserving pancreaticoduodenectomy, and those with ductal adenocarcinoma of the body or tail underwent distal pancreatectomy. All patients underwent dissection of lymph nodes, including nodes along the common hepatic artery (CHA) and SMA and the regional lymph nodes around the pancreas, while patients with pancreatic head cancer underwent dissection of the lymph nodes in the hepatoduodenal ligament in addition. Dissection of para-aortic lymph nodes was not routinely performed. The operative procedure generally included resection of the nerve plexus around the SMA (half on the tumor side), the nerve plexus around the CHA, and the celiac plexus. When the portal vein (PV) or SMV was involved, PV/SMV resection was performed if reconstructible. However, when the SMA, CHA, or celiac axis was definitively involved at operation, the tumor was considered unresectable, unless distal pancreatectomy with celiac axis resection for pancreatic body cancer that involved the celiac axis or the proximal part of the CHA could be performed for curative intent. Intraoperative pathological assessment of the pancreatic cut end margin was performed using frozen tissue sections. If the cut end margin was positive for adenocarcinoma, further resection of the pancreas was performed.

CT examination

All images were viewed on soft-tissue windows of MDCT. Two-phase abdominal contrast-enhanced CT (arterial and portal venous phase) was performed with 16-slice MDCT scanner in all patients before initial treatment. Images were reconstructed at 2-mm intervals using a standard soft-tissue algorithm. For interpretation of CT images, axial images were mainly assessed, but oblique-coronal MPR images

were assessed concurrently whenever available. All interpretations in terms of resectability were made by experienced surgeons and a radiologist according to the aforementioned criteria for BRPC.

Pathology investigations

Each resected pancreatic specimen was examined histologically for the histological type, tumor size, arterial invasion, PV invasion, nerve plexus invasion, bile duct invasion, duodenal invasion, serosal invasion, retroperitoneal invasion, nodal status, and margin status. Histological diagnosis was performed according to the TNM classification system of malignant tumors published by the International Union Against Cancer (UICC), 6th edition [8].

Postoperative adjuvant chemotherapy

No patients received postoperative adjuvant chemotherapy until 2007. Since 2007, 35 patients have received adjuvant chemotherapy consisting of three weekly intravenous infusions of gemcitabine 1,000 mg/m^2 followed by a 1-week pause for 6 months. Alternatively, 80 mg/m^2 of oral S-1 was given for 4 weeks, followed by a 2-week pause, for 6 months in 10 patients on a protocol designed for patients after resection of pancreatic adenocarcinoma.

Survival

Patients were followed regularly at 3-month intervals with blood testing and MDCT. Survival and follow-up were calculated from the time of the operation to the date of death or last available follow-up, and for LAPC patients, from the time of beginning first treatment. Cause of death and recurrence status were recorded. The survivors' median follow-up time after surgery was 26.4 months.

Statistical analysis

The χ^2 test and Student t test were used for univariate comparisons of clinicopathological factors except preoperative CA 19-9 level between subgroups based on resectability status. Mann-Whitney's U test was used to compare preoperative CA 19-9 level between subgroups. Analyses of survival were performed using the Kaplan–Meier method [9], and differences between the curves were tested using the log-rank test. Factors related to survival were analyzed with the Cox proportional hazards regression model [10]. A P value of <0.05 was considered significant. Statistical analysis was performed using SPSS version 17.0 software (SPSS, Chicago, IL, USA).

Results

MDCT findings for BRPC

During the period of this study, 24 of the 133 patients who initially underwent surgical resection for pancreatic ductal adenocarcinoma (i.e., BRPC-s) and 10 of the 185 patients who were initially treated as LAPC (i.e., BRPC-n) met the criteria for BRPC. Bilateral SMV/portal impingement was recognized in 11 patients (Fig. 1a, b), tumor abutment on the CHA in 7 (Fig. 1c), tumor abutment on the SMA in 16 (Fig. 1d), and tumor abutment on the celiac axis in 7.

Clinicopathological features of patients with BRPC

Table 1 summarizes the clinicopathological features of patients with resectable PC, BRPC, and unresectable PC. Tumor located in the head of the pancreas was significantly more frequent in patients with resectable PC than in those with BRPC ($P < 0.01$). Tumor size of BRPC was significantly greater than that of resectable PC ($P < 0.01$) and was significantly smaller than that of unresectable PC ($P < 0.01$). Preoperative CA 19-9 value seemed to increase as tumor resectability status progressed, but the differences were not significant.

Moreover, detailed pathological analyses were performed between resectable PC and BRPC-s. Tumor size of BRPC-s was 3.3 cm and tended to be greater than that of resectable PC ($P = 0.16$). Invasion of the artery, the PV, and the nerve plexus was seen in 14, 32, and 33 out of 109 resectable PC patients, and in 4, 14, and 18 out of 24 BRPC-s patients. Invasion of the PV and the nerve plexus was observed more frequently in BRPC-s than in resectable PC ($P < 0.01$). There was no significant difference in status of arterial invasion and invasion to other organs between the two subgroups. Patients with N1 were more frequently seen in BRPC-s patients ($n = 21$) than in resectable PC patients ($n = 81$), but the difference was not significant ($P = 0.19$). According to the TNM system [8], 1, 22, and 1 patients were diagnosed with stage IIA, IIB, and III disease, respectively, in BRPC-s patients, while 3, 25, 80, and 1 patients were diagnosed with IB, IIA, IIB, and III disease, respectively, in resectable PC patients.

Surgical resections of BRPC

In the BRPC-s group, subtotal stomach-preserving pancreaticoduodenectomy was performed in 15 patients, distal pancreatectomy in 4, distal pancreatectomy with celiac axis resection in 4, and total pancreatectomy in 1. In the 24 BRPC-s patients, 14 underwent SMV/PV resection, and 4 underwent celiac axis/CHA resection without reconstruction. The colon, jejunum, left adrenal gland, and left kidney

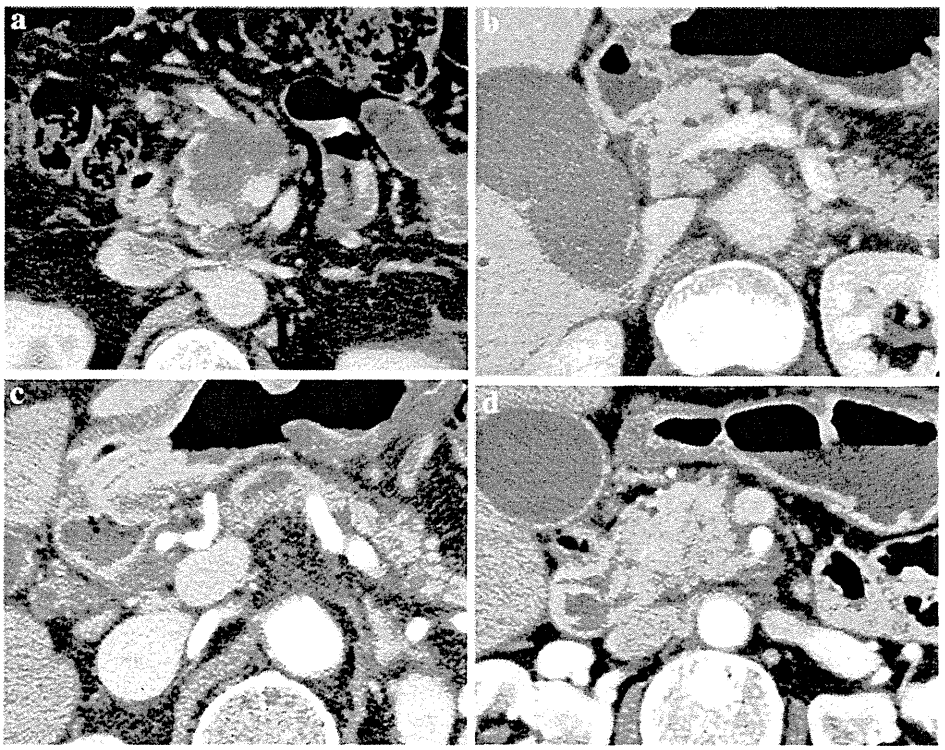

Fig. 1 Axial images from contrast-enhanced MDCT in patients with BRPCs. **a** Bilateral impingement of the SMV by the tumor located in the uncus. **b** Occlusion of a short segment at the confluence of the SMV and splenic vein. **c** Tumor abutment on the CHA. **d** Tumor abutment on the SMA with involvement of the root of the first jejunal artery

Table 1 Clinicopathological characteristics of patients with resectable PC, BRPC, and unresectable PC

Factor	Status of resectability			*P* value
	Resectable PC ($n = 109$)	BRPC ($n = 34$)	Unresectable PC ($n = 175$)	
Age, median (range) (years)	65 (34–85)	64 (40–84)	65 (34–85)	NS
Sex (*n*)				
Male	72	19	84	NS
Female	37	15	91	
Location of tumor (*n*)				
Head	77	17	90	<0.01*
Body or tail	32	17	85	
Histological type of tumor (*n*)				
Well	15	8	24	NS
Moderate/poor or others	94	26	84	
Not classified	0	0	67	
Tumor size, median (range) (cm)	2.8 (1.0–8.0)	3.5 (1.5–10.0)	4.1 (1.8–12.0)	<0.01**
CA 19-9, median (range) (U/ml)	106.0 (0.6–53,820)	191.5 (0.5–35,380.0)	339 (0.1–24,365.0)	NS

* Difference between resectable PC and BRPC

** Difference between resectable PC and BRPC, and between BRPC and unresectable PC

were also resected with pancreatic tumor in 2, 1, 1, and 1 patients, respectively. Positive microscopic surgical margins were more frequently seen in BRPC-s (7 of 24, 29%) than in resectable PC (21 of 109, 19%). However, the difference between the two groups was not significant ($P = 0.41$). There was no mortality. Eight postoperative complications were observed: five cases of pancreatic fistula, two cases of diarrhea, and one case of pleural effusion.

In the BRPC-n group, two patients underwent subtotal stomach-preserving pancreaticoduodenectomy for pancreas head cancer after systemic chemotherapy. One patient was alive with disease 35 months, and the other patient was alive without recurrence 21 months after beginning of the first treatment. Surgical resection was performed significantly more frequently in BRPC-n patients than in unresectable patients ($P < 0.01$).

Survival after resection of BRPC

The 2-year survival rates [estimated median survival time (MST)] of 109 patients with resectable PC, 34 patients with BRPC, and 175 patients with unresectable PC were 50.4% (24.6 months), 33% (15.7 months), and 13.5% (10.3 months), respectively (Fig. 2a). The prognosis of BRPC patients was significantly better than that of unresectable PC patients ($P < 0.01$), but was significantly worse than that of resectable PC patients ($P = 0.04$). In patients who initially underwent surgical resection for PC, survival was significantly shorter after resection of BRPC-s than after resection of resectable PC ($P = 0.03$) (Fig. 2b). On the other hand, in patients who were initially treated with nonsurgical therapy, the prognosis of BRPC-n was significantly better than that of unresectable PC patients ($P = 0.03$) (Fig. 2b).

Correlation between clinicopathological factors and overall survival in 133 PC patients who initially underwent resection

To identify prognostic factors for survival after resection of pancreatic ductal adenocarcinoma, clinicopathological factors and overall survival were analyzed in the 133 patients (Table 2). Maximum size above 3 cm ($P = 0.03$), nerve plexus invasion ($P < 0.01$), N1 ($P = 0.03$), SMV/portal impingement ($P = 0.02$), resectability ($P = 0.03$), and no adjuvant chemotherapy ($P < 0.01$) were significantly correlated with overall survival. The aforementioned factors were entered into multivariate analysis with a Cox proportional hazards model. Resectability was excluded from the analyses because it was strongly correlated with SMV/portal impingement. Nerve plexus invasion ($P < 0.01$), N1 ($P = 0.03$), and no adjuvant chemotherapy ($P = 0.02$) were predictors for decreased overall survival.

Recurrences after resection of BRPC

After surgical resection, 22 patients (92%) in the BRPC-s group and 75 (69%) in the resectable PC group developed recurrences. The locations of the initial recurrences in BRPC-s and resectable PC, respectively, were as follows: liver in 7 (29%) and 34 (31%); local recurrence in 10 (42%) and 23 (21%); lymph node in 4 (17%) and 13 (12%); peritoneum in 9 (38%) and 21 (19%); and other organs in 3 (13%) and 10 (9%). Local recurrence was more frequent in the BRPC-s group than in the resectable PC group ($P = 0.03$).

Postoperative adjuvant chemotherapy

Seven (29%) of 24 BRPC-s patients and 28 (26%) of 109 resectable PC patients received postoperative adjuvant chemotherapy. Gemcitabine was administered to 6 BRPC-s patients and 19 resectable PC patients, while S-1 was administered to 1 BRPC-s patient and 9 resectable PC patients. The median duration from operation to the start of adjuvant chemotherapy was 64 days in the BRPC-s patients and 56 days in the resectable patients (NS). Six (86%) BRPC-s patients and 19 (68%) resectable PC patients completed the 6-month course of adjuvant chemotherapy. Relative dose intensity of adjuvant chemotherapy was 85% in BRPC-s patients and 78% in resectable PC patients (NS).

Survival by postoperative adjuvant chemotherapy

In the resectable PC group, survival in patients with adjuvant chemotherapy (MST: not reached) was significantly better than that in patients without adjuvant chemotherapy (MST: 20.5 months) ($P < 0.01$). However, in

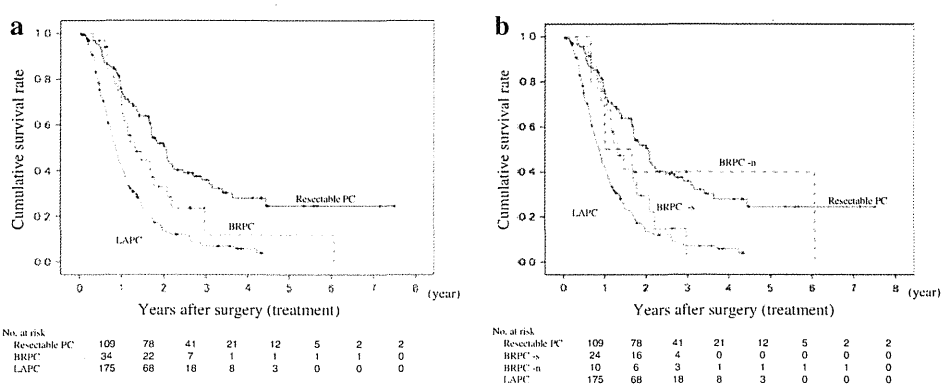

Fig. 2 **a** Comparison of survival in patients with resectable PC, BRPC, and unresectable PC. Both the differences between the resectable PC group and the BRPC group ($P = 0.04$) and between the BRPC group and the unresectable PC group ($P < 0.01$) were significant. **b** Cumulative survival curves according to detailed resectability status. Prognosis of BRPC-s was significantly worse than that of resectable PC ($P = 0.03$). Prognosis of BRPC-n was significantly better than that of unresectable PC ($P = 0.03$). *BRPC-s* BRPC treated with resection initially, *BRPC-n* BRPC treated with nonsurgical therapy initially

Table 2 Associations between overall median survival time (MST) and patient, tumor, and treatment characteristics in PC patients who were initially treated with surgical resection

Factor	MST (months)	Univariate analysis	Multivariate analysis	
		P value	Hazard ratio (95% CI)	*P* value
Age (years)				
<70	22.1	0.97		
≥70	20.8			
Tumor size				
≥3 cm	20.6	0.03	1.31 (0.84–2.05)	0.23
<3 cm	25.5			
CA 19-9				
≥200 U/ml	20.8	0.89		
<200 U/ml	25.0			
Portal vein invasion				
Present	21.6	0.196		
Absent	22.1			
Nerve plexus invasion				
Present	16.4	<0.01	2.33 (1.48–3.67)	<0.01
Absent	30.1			
Nodal status				
N1	20.5	0.03	1.89 (1.08–3.31)	0.03
N0	34.7			
SMV/portal impingement				
Present	12.8	0.02	1.72 (0.83–3.55)	0.15
Absent	25.0			
Tumor abutment on SMA, CE, or CHA				
Present	17.8	0.62		
Absent	22.1			
Status of resectability				
Borderline resectable	16.0	0.03	–	–
Resectable	25.0			
Resection status				
R0	22.4	0.09		
R1	21.6			
Adjuvant chemotherapy				
Yes	–	<0.01	0.49 (0.26–0.91)	0.02
No	20.8			

the BRPC-s group, the difference in survival between patients with adjuvant chemotherapy (MST: 20.3 months) and those without adjuvant chemotherapy (MST: 13.7 months) was not significant ($P = 0.54$).

Discussion

Borderline resectable pancreatic cancer is a newly proposed subset that shows interactions with the PV, SMV, SMA, celiac axis, and hepatic artery, and may have a high possibility of a positive surgical margin and worse prognosis after resection [1–3]. In the report of the AHPBA/SSO/SSAT Consensus Conference, it was recommended that patients with BRPC receive neoadjuvant therapy to increase the possibility of R0 resection in a clinical trial setting specific for BRPC patients [7]. As the rationale for the recommendation, the MD Anderson Cancer Center group demonstrated that neoadjuvant therapy enabled margin-negative resection in 37%, with median survival after resection of 40 months in the 84 patients with anatomical BRPC as defined on CT [2]. Chun et al. [11] also reported significantly better survival (23 vs. 15 months) and a higher R0 resection rate (59 vs. 11%) in 74 BRPC patients with preoperative chemoradiation than in 35 BRPC patients without preoperative therapy. However, little has been reported on the difference in surgical results, including prognosis and positive surgical margin rate,

between resectable PC and BRPC that might support the use of neoadjuvant therapy specific for BRPC patients. Furthermore, prognosis of BRPC patients initially treated with nonsurgical treatment such as chemotherapy or chemoradiotherapy has not been well documented.

In the present study, MDCT findings before initial treatment of all resected PC patients and all patients treated for LAPC were assessed for the possibility of BRPC because BRPC should be diagnosed before initial treatment to determine the treatment plan. BRPC was sub-classified into two types: BRPC-s, which was initially treated with resection, and BRPC-n, which was initially treated with nonsurgical therapy. Prognosis of all 34 BRPC patients was significantly worse than that of resectable PC patients and significantly better than that of unresectable PC patients. Moreover, in patients who initially underwent resection, prognosis of patients with BRPC-s was significantly worse than that of resectable PC patients, and in patients who were initially treated with nonsurgical therapy, prognosis of BRPC-n was significantly better than that of unresectable PC patients.

As possible reasons for the worse prognosis of BRPC-s than that of resectable PC, BRPC-s had a high rate of positive PV invasion and nerve plexus invasion compared to resectable PC ($P < 0.01$). Moreover, BRPC-s tended to show a more advanced stage in nodal status ($P = 0.19$) and tumor size ($P = 0.16$) than resectable PC. Nerve plexus invasion and lymph node metastasis were the independent poor prognostic factors in all 133 resected PC patients. The poor prognosis of BRPC-s patients was primarily attributable to these advanced characteristics. In terms of resection status, patients with BRPC-s had a positive surgical margin rate 10% higher than that of resectable PC patients, but the difference was not significant ($P = 0.41$). Interpretation of the 10% difference in the R0 rate between BRPC-s and resectable PC was difficult when evaluating how much the poor prognosis of BRPC-s patients was due to the difference in the R0 rate, considering both the lesser prognostic value of margin status and the frequent recurrence at locoregional sites in the BRPC-s patients. With respect to the surgical margin, there are no international standardized protocols for processing pancreatic specimens or criteria for positive margins [12, 13], and the relevance of margin status for prognosis is not clear in resected PC patients [6, 14–18]. An international standardized protocol for the histological examination of the surgical margins of pancreatic specimens is needed to prepare comparable data.

Nerve plexus invasion is a distinctive type of tumor spread in pancreatic ductal carcinoma, and it is also known to be a poor prognostic factor after tumor resection [19–21]. The nerve plexus of the pancreatic head runs from the pancreas to the celiac or superior mesenteric plexus along the celiac axis and SMA [22, 23]. Considering the anatomy, it is understandable that BRPC invades the nerve plexus quite frequently. Mochizuki et al. [24] reported that the mass and strand pattern and the coarse reticular pattern continuous with tumor on MDCT images are highly suggestive of nerve plexus invasion. Taking these results into account, tumor abutment on the arteries in BRPC could represent mostly nerve plexus invasion along those arteries. The higher R1 rate and frequent local recurrence in BRPC-s patients could be partly due to nerve plexus invasion.

Curiously, the prognosis of BRPC-n was significantly better than that of unresectable PC in patients who were initially treated with nonsurgical therapy. Less tumor burden as shown in tumor size and CA 19-9 value could mostly account for the better prognosis of patients with BRPC-n than that of patients with unresectable PC. In addition, surgical resection after down-staging by nonsurgical therapy was performed significantly more frequently in the BRPC-n group than in the unresectable PC group. Frequent conversion from nonsurgical therapy to surgical resection might also be one of the possible reasons for better survival of patients with BRPC-n. However, assessment of tumor resectability during nonsurgical treatment was not performed systematically or thoroughly for BRPC-n patients or unresectable PC patients in this study. Thus, the resectability rate of BRPC patients and unresectable PC patients was not definitive in the present study. In order to investigate conversion rate from nonsurgical therapy to surgical resection, systematic assessment for resectability during nonsurgical treatment is required although criteria of resectability after treatment have not been clarified. Owing to the different backgrounds and prognoses between BRPC and unresectable PC, they should be regarded as different categories.

Similar to the AHPBA/SSO/SSAT Consensus Conference recommendation [7], we reached the conclusion that neoadjuvant therapy such as chemoradiation for BRPC should be evaluated separately from those for resectable PC or unresectable PC for several reasons. First, patients with BRPC-s had poorer survival and more frequent recurrence at the local site than patients with resectable PC. Thus, patients with BRPC should be treated with more intensive therapy with strong local effect rather than the existing treatment for resectable PC. Second, neoadjuvant therapy could benefit patients with BRPC by providing early treatment for those with advanced disease at high risk of early systemic and local failure [2, 7]. Several phase II studies showed the possibility of neoadjuvant chemotherapy [25] or chemoradiation [26] for BRPC. Furthermore, adjuvant chemotherapy might not be as effective in BRPC patients as in resectable PC patients according to the results of the present study, although multi-institutional randomized controlled study is needed to clarify the effectiveness of adjuvant treatment for BRPC. Adjuvant chemotherapy

with gemcitabine or S-1 was a favorable prognostic factor for all 133 resected PC patients. However, in BRPC-s, the prognosis of patients with adjuvant chemotherapy was as poor as that of patients without adjuvant chemotherapy, while the duration from surgery to start of adjuvant treatment and relative dose intensity of adjuvant treatment did not differ between BRPC-s patients and resectable PC patients. Third, BRPC should be studied separately from unresectable PC because of the different tumor characteristics and prognoses. BRPC is more often resectable than unresectable PC, thus resectability status should be assessed systematically and thoroughly.

The limitations of our study are its retrospective design and the relatively small number of patients studied.

In conclusion, patients with BRPC showed more advanced tumor characteristics, including frequent nerve plexus invasion, frequent loco-regional recurrence, and poorer prognosis than patients with resectable PC although BRPC had less tumor burden and better prognosis than patients with unresectable PC. Neoadjuvant treatment with intensive local and systemic effect that is specific for BRPC is required. A multi-institutional phase II trial of neoadjuvant chemoradiation for BRPC is now in the planning stage.

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Treatment Strategy for Superficial Pharyngeal Squamous Cell Carcinoma Synchronously Combined with Esophageal Cancer

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Key Words
Pharyngeal cancer · Chemotherapy · Esophageal squamous cell carcinoma · Narrow band imaging · Early detection

Abstract
Background: Esophageal squamous cell carcinoma (ESCC) is often synchronously accompanied by pharyngeal squamous cell carcinoma (PSCC). However, treatment strategies for these synchronous cancers have not been established. ***Aim:*** To evaluate retrospectively the effects of both chemoradiotherapy (CRT) targeted for invasive ESCC on synchronous superficial PSCC and additional endoscopic resection (ER) for PSCC. ***Patients and Methods:*** Screening endoscopy in the pharynx was performed in newly diagnosed ESCC patients. CRT combined with 5-fluorouracil (5-FU) and cisplatin (CDDP) was administered to all patients. The effect on superficial PSCC was only evaluated for 5-FU-CDDP chemotherapy that excluded the pharynx from the radiation field. When PSCC was remnant or recurrent in patients evaluated at complete response (CR) of ESCC, ER was performed on the PSCC. ***Results:*** Fourteen cases of superficial PSCC (4.0%) were detected in 348 ESCC patients. Three PSCC reached CR in 8 ESCC-CR patients, while all 3 lesions recurred. No treatment response was found in the remaining 11 PSCC. As a second treatment, ER for 8 PSCC was completed in the 8 ESCC-CR patients, with one complication due to pneumonia. ***Conclusions:*** Standard 5-FU-CDDP CRT targeted for invasive ESCC did not demonstrate a sufficient efficacy for superficial PSCC, while ER even for PSCC after chemotherapy was curative.

Introduction

Esophageal squamous cell carcinoma (ESCC) is often accompanied by pharyngeal squamous cell carcinoma (PSCC) either simultaneously with the primary lesion (synchronously) or after a period of time (metachronously). These findings have been explained by the 'field cancerization' theory that describes how repeated local exposure to carcinogens contributes to the occurrence of multiple cancers in the esophageal and head and neck regions [1]. For more than 5 decades many epidemiological studies have attributed the increased cancer risks associated with alcohol drinking and smoking to this phenomenon

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[2–6]. In 2009, the Working Group of WHO-IARC concluded that acetaldehyde associated with alcoholic beverages was carcinogenic to humans and confirmed the group 1 classification of alcohol consumption [7]. In addition, heterozygous traits found in 40% of Asians, who have an inactive alcohol metabolizing enzyme of aldehyde dehydrogenases 2, accumulate acetaldehyde, with higher relative risks of these cancers [7, 8]. Furthermore, the prevalence of multiple Lugol-unstained lesions (LULs) [9, 10], which are caused by repeated exposure to acetaldehyde, was strongly related to the occurrence of synchronous or metachronous cancers in the esophagus and head and neck regions [11].

In contrast, most patients with PSCC are detected at an advanced stage with a poor prognosis. Even in an operable PSCC case, the extensive surgical resection required may cause a loss of function with respect to swallowing and/or speaking and can lead to cosmetic deformities. Thus it is difficult to determine a final treatment from the viewpoints of both curability and retaining organ function. In cancers combining ESCC and PSCC, the selection of treatment is even more critical. Because of this, the ability to detect pharyngeal lesions at an earlier stage, e.g. as carcinoma in situ, would be of clear benefit to patients. Recently, superficial PSCC has been detected by NBI endoscopy [12].

Systemic 5-fluorouracil-cisplatin (5-FU-CDDP) chemotherapy combined with radiotherapy is the standard treatment for ESCC, and the same treatment is also effective for PSCC patients [13, 14]. The radiation field used in radiotherapy for ESCC does not generally reach the region of the larynx and pharynx, while chemotherapy acts systemically. There have been no reports regarding the efficacy of systemic chemotherapy for patients with superficial PSCC. In this study, we examined the effect on superficial PSCC of chemoradiotherapy (CRT) targeted for invasive ESCC.

Patients and Methods

Patients

Between January 2003 and December 2006, concurrent CRT was performed in 348 patients with invasive ESCC who met the following criteria of this study: (1) newly diagnosed thoracic ESCC; (2) aged between 20 and 75 years; (3) clinical stage I to IVA according to the UICC-TNM classification; (4) absence of previous chemotherapy for malignancy; (5) absence of radiation or surgical treatment for head and neck, and esophageal cancers, and (6) absence of active malignancy except ESCC and PSCC. All patients with invasive ESCC visited our hospital to receive treatment after histological diagnosis of ESCC by endoscopy at another hospital.

Endoscopic Observation of the Oral Cavity and Pharynx

Since January 2003, endoscopic screening of the oral region has been performed in all ESCC patients in order to detect synchronously superficial PSCC. In the initial endoscopic observation in our hospital, narrow band imaging (NBI) or conventional endoscopy was used because both evaluation of ESCC and gastroduodenal screening including oral cavity and pharynx are performed in all patients. When a mucosal abnormality in the oral cavity or pharynx, or multiple LULs in the esophagus, were found in initially conventional endosopcy, the oral cavity and pharynx were observed again by magnifying NBI endoscopy within 2 weeks. Figure 1 shows the NBI findings of an oral cavity and pharynx using a video endoscope system (EVIS LUCERA CV-260, Olympus Optical Co. Ltd., Tokyo, Japan). When a brownish area and an enhancement of the intraepithelial papillary capillary loop were found in the pharynx (fig. 2), an endoscopic biopsy was performed to histologically confirm the carcinoma.

Lugol chromoendoscopy was performed in all patients for both diagnosis of the correct cancer region and evaluation of LULs in the background esophageal epithelium. After ordinary endoscopic observation, 5–10 ml of 2.0% glycerin-free Lugol iodine solution, which is a brown liquid consisting of 2.0 g potassium iodine and 4.0 g iodine in 100 ml distilled water, was sprayed from the upper thoracic esophagus to the gastroesophageal junction using a plastic spray catheter passed through the biopsy channel of the endoscope. Multiple LULs were defined as described in our previous study [15].

Definition of Superficial Pharyngeal Cancer

According to the Japan Society for Head and Neck Cancer [16], a superficial pharyngeal lesion is defined as one in which the invasion depth is comparatively limited and visual changes do not indicate an advanced cancer. The pharynx has no muscularis mucosa, so this somewhat vague definition suggests that the depth of invasion is limited to the epithelium or just beneath the epithelium, but does not extend to the muscle layer.

Treatment Schedule of CRT for ESCC

Chemotherapy consisted of a protracted infusion of 5-FU at a dose of 1,000 mg/m^2 per day on days 1–5 and 22–26, combined with a 2-hour infusion of CDDP at 75 mg/m^2 on days 1 and 22. A 10-MV radiation treatment was administered for 6 weeks (5 days/week) at 1.8 Gy/day with a total radiation dose of 50.4 Gy, concomitantly with chemotherapy.

Patients who were evaluated for an objective response to this treatment received additional chemotherapy consisting of a continuous infusion of 5-FU at a dose of 1,000 mg/m^2 on days 1–5 and CDDP at a dose of 75 mg/m^2 on day 1. This treatment schedule was administered for 1 week followed by a 3-week break. All patients receiving CRT were monitored by neck, chest and abdominal computed tomography, and by endoscopy to evaluate the efficacy of the treatment on both ESCC and PSCC.

As for response for ESCC, objective responses of measurable metastatic lesions were evaluated according to the response evaluation criteria in solid tumors (RECIST v 1.0) guideline. Response of the primary tumor was evaluated by the criteria of the Japan Esophageal Society [17, 18].

Evaluation of Response for PSCC

All follow-up evaluations after 5-FU-CDDP chemotherapy for PSCC were performed every 2 months for the first year and every 6 months thereafter by magnifying NBI endoscopy, with the same periods of evaluation as for ESCC. For PSCC, complete response (CR) was defined as the disappearance of all visible tumors (brownish areas), including ulceration, for at least 4 weeks, confirmed by normal endoscopic biopsy specimens. The recurrence was defined as the reappearance of a brownish area accompanied by an enhancement of intraepithelial papillary capillary loop by NBI endoscopy, and was confirmed in histological findings by endoscopic biopsy. Non-CR for PSCC was defined as the remnant of brownish areas and was classified into a partial response, stable disease or progressive disease.

In the case of non-CR for PSCC, the second treatment was selected according to the efficacy of CRT for ESCC. When ESCC reached CR with remnant or recurrence of PSCC, endoscopic resection (ER) was performed for PSCC. When the ESCC was evaluated for non-CR, thereafter treatment for ESCC, such as second-line chemotherapy, salvage surgery or palliation was performed.

ER for PSCC after CRT

The ER involved endoscopic mucosal resection using the cup method or an endoscopic subepithelial dissection method with the patient under general anesthesia. An important consideration was that ER for PSCC should be performed with cooperation from the endoscopists and the head and neck surgeons. Some head and neck surgeons participated in the ER to prepare emergency treatment, such as tracheostomy, with evaluation of the degree of laryngeal edema after the procedure.

Statistics

All statistical analyses were performed using IBM SPSS Statistics 18 software (SPSS Inc., Tokyo, Japan). Overall survival data were calculated from the date of commencement of CRT to the date of death or the most recent follow-up visit. Survival curves were plotted according to the Kaplan-Meier method. The significance of differences was assessed using the log-rank test. A p value of <0.05 was considered statistically significant.

Results

Patient Characteristics

Fourteen patients (4.0%) with synchronous superficial PSCC were found among the 348 patients with invasive ESCC (table 1). Of the 14 patients, 13 (93%) were male and the median age was 62 years. The number of patients for ESCC clinical stage I, II, III, and IVA were 5, 2, 6 and 1, respectively. All 14 patients had both daily alcohol consumption and multiple LULs of the esophagus. All PSCC lesions were detected at our institute with no prior detection in other hospitals. Twelve (86%) PSCC lesions were detected using magnifying NBI endoscopy and the other 2 (14%) by conventional endoscopy. The latter 2 lesions were reevaluated with magnifying NBI endoscopy before

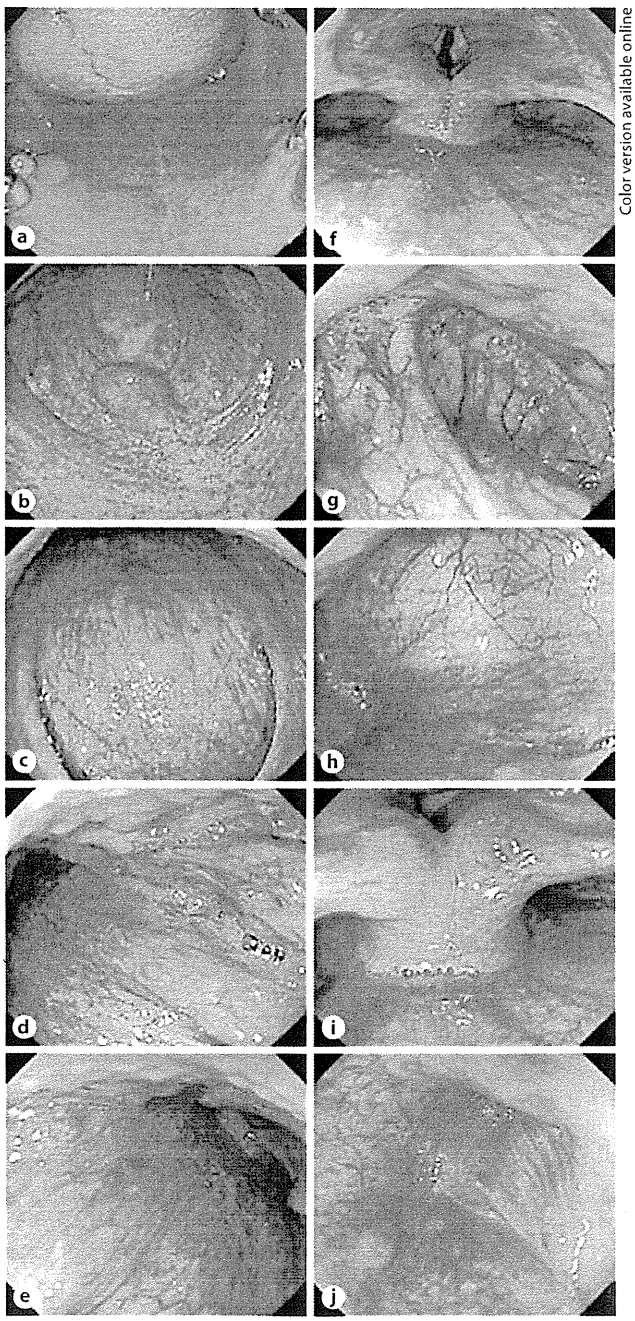

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Fig. 1. Narrow Band Imaging observations in individual regions from the oral cavity to the pharynx. **a** The view seen from the entrance of the oral cavity: dorsal side of tongue, hard palate and soft palate. **b** Uvula, palatoglossal arch and lateral walls of oropharynx. **c** The posterior wall of oropharynx. **d** The right side of base of tongue and lateral wall of oropharynx. **e** The left side of base of tongue and lateral wall of oropharynx. **f** Posterior wall of hypopharynx and larynx. **g** Vallecula of epiglottis, median glossoepiglottic fold. **h** The lateral wall and apex of right piriform sinus. **i** Arytenoids. **j** The lateral wall and apex of left piriform sinus.

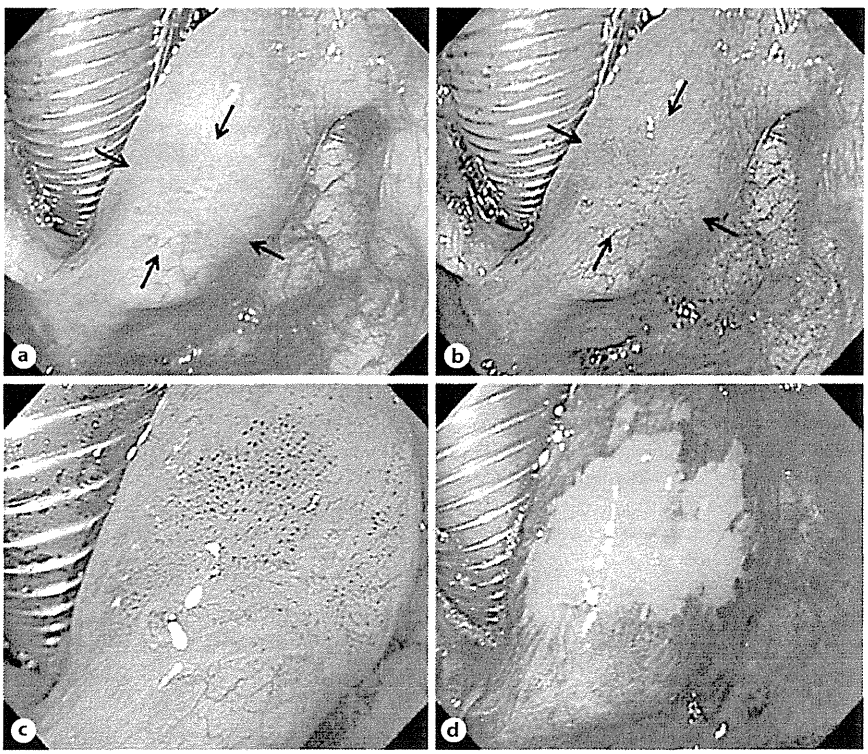

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Fig. 2. Superficial cancer of the right arytenoid. **a** Conventional endoscopic observation. The margin of the cancer is unclear (black arrows). **b** NBI observation. Cancer is shown as a brownish area (black arrows) and the margin is clear. **c** Magnifying NBI observation. The enhanced intraepithelial papillary capillary loop is seen in the cancer area. **d** The view of Lugol staining. Lugol-unstained lesion coincided with the cancer area. Lugol staining method was used to improve lesion visualization during endoscopic treatment. Color refers to the online version only.

Table 1. Patient characteristics

Age, years	Median	62
	Range	47–71
Gender	Male	13
	Female	1
Alcohol consumption	Presence	14
	Absence	0
Cigarette smoking	Presence	12
	Absence	2
Multiple LULs	Presence	14
	Absence	0
PSCC		
Location	Hypopharynx	10
	Oropharynx	4
Size, mm	Median	20
	Range	5–50
Macroscopic findings	Elevated type	5
	Flat type	4
	Depressed type	5
ESCC		
Clinical stage	I	5
	II	2
	III	6
	IVA	1

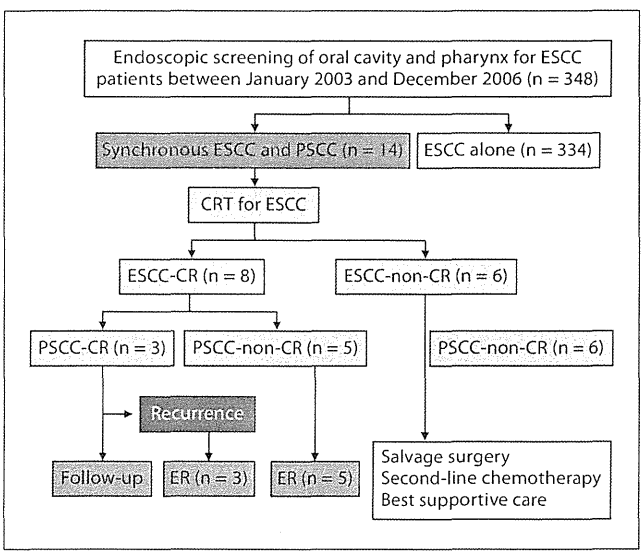

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Fig. 3. Flow chart of this study.

CRT. The majority of PSCCs were located in the hypopharynx. In macroscopic findings, there were various lesion types. The median lesion diameter was 20 mm, ranging from 5 to 50 mm. All PSCC lesions were superficial cancers with no advanced cancers.

Efficacy of 5-FU-CDDP Chemotherapy for PSCC

The treatment for PSCC was determined according to response to CRT for primary ESCC (fig. 3). CRT for ESCC resulted in CR in 8 of the 14 patients. In contrast, only 3 of 14 PSCC lesions were evaluated as CR. The 3 PSCC-CR lesions (38%) were found in the ESCC-CR patients (fig. 3). However, the 3 PSCC-CR lesions were only transiently disappeared, and local recurrence was found in the same region. In the 6 ESCC-non-CR patients, there were no PSCC-CR lesions. Of the 6 patients, 2 who were finally evaluated as partial response for ESCC had transformation of their superficial PSCC to invasive lesions. Therefore, active salvage surgery with laryngopharyngeal and esophageal resection was undertaken in these 2 patients. Of the remaining 4 patients, 2 lesions had no change in size and shape while the other 2 were evaluated as partial response because of decreased tumor size.

ER for PSCC and Complications

ER for PSCC was performed in the 8 patients with ESCC-CR. Histologic findings showed the depth of infiltration was invasive PSCC in 2 patients and cancer in situ in 6 patients. However, no lymphovascular involvement was found in any of the 8 cases with PSCC.

Major complications associated with ER included 1 case of aspiration pneumonia. There were no severe complications such as subcutaneous emphysema, post-ER stricture or delayed bleeding. Of the 8 PSCC lesions, 1 was recurrent 4 months after ER. Because the recurrent lesion was superficial and small, an additional ER was performed with complete resection. The median duration of follow-up after ER was 28 months ranging from 12 to 39 months, and no more recurrences of the PSCC were found.

Survival

The 8 ESCC-CR patients received ER for PSCC and the remaining 6 ESCC-non-CR patients did not. The pretreatment clinical stages of ESCC in 8 ER and 6 non-ER patients were 4 and 1 patient in stage I, 1 and 1 in stage II, 2 and 4 in stage III and 1 and 0 in stage IVA, respectively. There were no differences in clinical staging variety in the ESCC pretreatment evaluation between ER and non-ER patients. Median survivals of ER and non-ER patients were 51 and 14 months, respectively (p = 0.002; log-rank test; fig. 4). The 3-year survival rates of ER and non-ER patients were 63 and 0%, respectively. In contrast, 4 of the 8 ER patients died during follow-up periods. Preclinical stages of the 4 patients were 2 patients in stage I, 1 in stage II and 1 in stage IVA, respectively. The 2 patients in stage I died of radiation-induced pneumonia and cerebral infarction. The patient in stage II died of ESCC progression with lymph node metastases and the remaining patient in stage IVA died of multiple lung metastases.

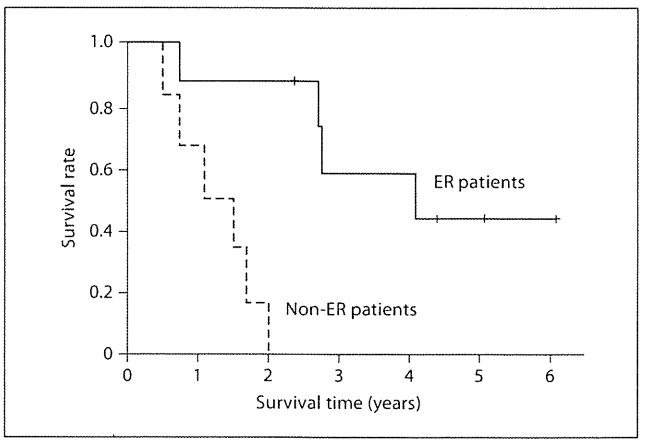

Fig. 4. Overall survival. Median survivals of ER and non-ER patients were 51 and 14 months, respectively (p = 0.002; log-rank test).

After CR confirmation in ESCC, ER was performed in PSCC. The median duration from commencement of CRT to ER in the 8 patients receiving ER was 5.4 months, ranging from 3.8 to 18.9 months. ER was performed in 5 of the 8 patients immediately after CRT since PSCC lesions of the 5 patients were not evaluated as CR. However, the time periods to perform ER after CRT were extended in the remaining 3 PSCC-CR patients from 10 to 18.9 months due to following-up for PSCC-CR. There were no cases in which superficial PSCC transformed to an advanced stage during the follow-up periods. Thus, no functional disorder caused by progression of PSCC, such as difficulty swallowing or speaking, were found in ER patients during all follow-up periods.

Discussion

Of 348 patients with invasive ESCC, 14 (4%) had superficial PSCC detected through endoscopic screening of the oral cavity and pharynx. Standard 5-FU-CDDP CRT targeted for invasive ESCC was administered to the 14

patients with synchronous superficial PSCC and invasive ESCC. After CRT, 8 (57%) were evaluated as CR for invasive ESCC, while only 3 patients with superficial PSCC (21%) achieved transient CR despite receiving 5-FU-CDDP chemotherapy. Therefore, systemic 5-FU-CDDP chemotherapy had no CR potential for superficial PSCC. In contrast, ER for superficial PSCC is quite effective even in a situation after chemotherapy because of minimally invasive treatment with no functional disorder in the pharyngeal region. We propose using novel treatment strategies for synchronous superficial PSCC and invasive ESCC.

Acetaldehyde associated with alcoholic beverage and aldehyde dehydrogenases 2 heterozygous traits can cause pharyngeal and esophageal cancers [7]. According to recent reports regarding multiple cancers, the prevalence of multiple LULs is a biomarker of synchronous or metachronous cancers in the esophagus and head and neck regions [19–21]. In our present study, all 14 patients with synchronous ESCC and PSCC had both daily alcohol consumption and multiple LULs in their esophageal background epithelium. Lugol chromoendoscopy is useful not only to detect superficial ESCC but also to understand the risk of multiple cancers. However, the Lugol solution cannot be routinely sprayed in the region of the pharynx and larynx of patients under conscious sedation because of the stimulation caused by the application of the solution. Thus, we suggest that detecting superficial PSCC by NBI is useful in ESCC patients, especially those with both an alcohol drinking habit and multiple LULs in their esophagus.

5-FU-CDDP treatment has been performed in PSCC patients since the 1980s. The CR rate of this therapy without radiotherapy was 17–20% of locally advanced or metastatic PSCC cases in phase I–II studies [13, 14], and was 5–7% of metastatic or recurrent cases in phase III studies [22, 23]. 5-FU-CDDP treatment alone is likely to be more effective in locally advanced PSCC than in metastatic PSCC. In contrast, there has been no study of 5-FU-CDDP alone in PSCC of early clinical stage, especially stage 0–I. Therefore, the 5-FU-CDDP treatment efficacy in superficial PSCC is uncertain. If the therapy had a high efficacy for superficial PSCC, overlooked superficial PSCC would be cured by the systemic 5-FU-CDDP therapy given to treat ESCC. This is quite a benefit for the patients with these synchronous cancers. As a result, PSCC-CR was found, while no efficacy in continuing CR for superficial PSCC was found in 5-FU-CDDP treatment. In contrast, no progression of PSCC was found in patients having excellent efficacy with CRT for ESCC, although the time periods until CR confirmation for ESCC were required to be at least several months. A good correlation in treatment efficacy between PSCC and ESCC was indicated. It seems that 5-FU-CDDP chemotherapy has a potential in restraining the progression of PSCC. In some recent reports, platinum-based chemotherapy or CRT plus cetuximab were more effective in esophageal and the head and neck cancers [24–26]. CRT combined with cetuximab, a molecular targeted drug, may contribute to a novel treatment strategy for patients with synchronous PSCC and ESCC.

The outcomes of ER for superficial PSCC have been reported [27]. Complications, such as laryngeal edema requiring overnight intubation, aspiration pneumonia and sustained dermatitis around the mouth caused by backflow of Lugol solution from the pharynx, were found in 13% of patients after ER [27]. Complications are transient and tolerable in most of cases, and feasibility is confirmed with no functional disorder. In our study, there were no severe complications, with high treatment efficacy for ER during long follow-up periods, although ER was performed in the condition after 5-FU-CDDP chemotherapy. It is important to maintain function with respect to swallowing and/or speaking, and to perform ER under cooperation with head and neck surgeons.

Regarding the treatment strategy, CRT for ESCC should be the initial therapy in patients with both superficial PSCC and ESCC. As the second step, ER for PSCC should be determined after evaluation of CRT for ESCC. A factor deciding the prognosis of patients with the synchronous cancers depends on the CRT effects for ESCC. In our previous study, the prognosis between CR and non-CR cases of ESCC was quite different [28]. In our present study, the median survival time of ER (ESCC-CR) patients was also significantly longer than that of non-ER (ESCC-non-CR) patients. Furthermore, 5-FU-CDDP chemotherapy showed potential in restraining the progression of PSCC including transient CR. If ER was performed initially, the period before commencement of CRT would be delayed. In addition, when complications occurred in ER, the commencement would be further delayed. Therefore, ER for superficial PSCC should be secondary to CRT for invasive ESCC. We suggest that the ER for PSCC contributed to the beneficial prognosis in patients with synchronous superficial PSCC and invasive ESCC. It is uncertain whether all superficial PSCC lesions progress to an advanced stage in the natural history. However, if superficial PSCC was overlooked and progressed to an advanced stage in ESCC-CR patients, it would be difficult to achieve long survival. Furthermore,

when the patients with advanced PSCC receive active treatments, such as surgery or CRT, functional disorder of swallowing or speaking might occur. On this point, ER for superficial PSCC can prevent a progression to an advanced stage, with favorable prognosis.

In our present study, not all patients received magnifying NBI endoscopy in their initial pretreatment evaluation, while superficial PSCC was detected in 4% of 348 patients with newly diagnosed ESCC. From the results of previous studies, Shimizu et al. [29] proposed that superficial PSCC was metachronously found in 2% of ESCC patients receiving EMR through laryngoscopy. Katada et al. [30] reported that superficial PSCC was found in 11% of patients with previous or current ESCC through magnifying NBI observation. In our study, 12 (86%) of the 14 cases of superficial PSCC were detected by magnifying NBI observation. We emphasize that NBI endoscopy in the oral region should be performed in ESCC patients to detect superficial PSCC. A recent report of a multicenter trial suggested that NBI should be the standard examination for the early detection of superficial cancer in the esophagus and head and neck [12]. Furthermore, we demonstrated that magnifying NBI endoscopy was effective in following up patients after treatment since we could detect a transient lesion disappearance or a minor local recurrence. We suggest that NBI should be used not only in the screening observation of the pharynx but also for follow-up endoscopy after treatment with 5-FU-CDDP chemotherapy or ER. However, a limitation is that our study was a single-institute retrospective study.

In conclusion, systemic chemotherapy for superficial PSCC was regrettably found to have no potential in continuing CR, while CRT as targeted to ESCC led to control of superficial PSCC progression. In the present condition, the detection of superficial PSCC is important in making a treatment strategy for synchronous PSCC and ESCC. One of the treatment strategies in patients with the synchronous cancers was that CRT for invasive ESCC should precede ER for superficial PSCC, and that the treatment of superficial PSCC should be decided according to the efficacy of CRT for ESCC. ER for superficial PSCC caused no functional disorders and was effective in curing even the lesions remaining after 5-FU-CDDP chemotherapy. We suggest that curative ER contributes to a beneficial prognosis in patients with ESCC-CR and believe a large-scale clinical trial will be required to establish treatment strategies.

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Disclosure Statement

The authors declare no conflict of interest.

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Photodynamic therapy as salvage treatment for local failure after chemoradiotherapy in patients with esophageal squamous cell carcinoma: A phase II study

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Local failure at the primary site is a major problem after chemoradiotherapy (CRT) in patients with esophageal squamous cell carcinoma (ESCC). Salvage surgery is the only treatment option with curative intent, but it is associated with high morbidity and mortality. The aim of this study was to evaluate the efficacy and safety of salvage photodynamic therapy (PDT) after CRT. Patients with histologically proven local failure limited to the submucosal layer, and without any metastasis after definitive CRT (≥50 Gy) for ESCC were enrolled in the study. PDT began with intravenous administration of 2 mg/kg of porfimer sodium followed 48–72 hr later by excimer dye laser irradiation with a fluence of 75 J/cm^2. The primary endpoint was a complete response (CR) to treatment with PDT, and the secondary endpoints were toxicity related to PDT, progression-free survival (PFS) and overall survival (OS). Twenty-five patients were enrolled in the study. A CR was attained in 19 of 25 patients treated with PDT (CR rate, 76%; 95% CI, 55–91%). One treatment-related death (4%) caused by gastrointestinal hemorrhage at the irradiated site occurred 33 days after PDT. No adverse events greater than grade 3 were related to PDT in the other patients. After a median follow-up of 48 months after PDT, the PFS and OS at 3 years were 40% (95% CI, 21–59%) and 38% (95% CI, 17–60%), respectively. PDT is a potentially curative and tolerable salvage treatment after CRT for carefully selected patients with local failure without any metastasis.

Chemoradiotherapy (CRT) is a curative treatment option for esophageal squamous cell carcinoma (ESCC). However, local failure without distant metastasis after completion of CRT remains a major problem that must be overcome to achieve a cure. Although salvage esophagectomy is now indicated for such patients, it has a higher morbidity and mortality compared with primary or planned esophagectomy.[1–4] The development of curative and safe salvage treatment options for local failure is needed to improve the survival of patients treated with CRT.

Key words: esophageal squamous cell carcinoma, chemoradiotherapy, photodynamic therapy, salvage treatment
Abbreviations: CR: complete response; CRT: chemoradiotherapy; EMR: endoscopic mucosal resection; ESCC: esophageal squamous cell carcinoma; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs: non-steroidal anti-inflammatory drugs; OS: overall survival; PDT: photodynamic therapy; PFS: progression-free survival; UMIN: University hospital Medical Information Network
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After completion of CRT, a subset of ESCC patients develops local failure at the primary site without distant metastasis. In such patients, salvage surgery could be a curative treatment option, especially for those with T2 or earlier T-stage tumors or for those without lymph node metastasis.[1,2] Onozawa *et al.* reported that regional nodal failure within the field of elective lymph node irradiation is rare in patients achieving a complete response (CR) after CRT (1%; 95% CI, 0.0–5.3%).[5] These data have encouraged the use of local salvage treatment at only the primary site as a minimally invasive treatment in carefully selected patients.

We reported previously on the potentially acceptable results of endoscopic mucosal resection (EMR) or photodynamic therapy (PDT) as a salvage treatment for local failure after CRT.[6–8] PDT is a more deeply penetrating method than EMR for esophageal cancer even in the salvage setting, because, in our experience, PDT can cure patients with deep invasion of the submucosal layer or T2 local failure. In addition, PDT can be indicated both as a curative treatment for superficial esophageal cancer[9,10] and as a palliative treatment to relieve dysphagia caused by stenosis in more advanced esophageal cancer.[11] We believe that PDT might be a curative and effective treatment option for patients with local failure at the primary site after definitive CRT. We conducted a prospective study to evaluate the efficacy and safety of salvage PDT after CRT.

Material and Methods

This was a single-arm, open-label, single-center phase II study. The primary endpoint of this study was the CR rate at the primary site after PDT. The secondary endpoints were toxicity related to salvage PDT, progression-free survival (PFS) and overall survival (OS). All adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.[12] The study protocol was approved by the institutional review board of the Japanese National Cancer Center in January 2005. The study was carried out according to the ethical principles of the Declaration of Helsinki. Before enrollment, all patients provided written informed consent. This study was registered with the University hospital Medical Information Network (UMIN) Clinical Trials Registry, and the identification number is C000000244.

Eligibility and exclusion criteria

The eligibility criteria of this study were as follows: (*i*) local failure after definitive CRT ($\geq$50 Gy) for ESCC; (*ii*) the patient's refusal to undergo salvage surgery; (*iii*) histologically proven squamous cell carcinoma by biopsy specimen of the local failed lesions; (*iv*) local failed lesions limited to the submucosal layer; (*v*) EMR not indicated for reasons of concomitant deep ulceration, severe fibrosis caused by radiation or a lesion invading to the deep submucosal layer; (*vi*) Eastern Cooperative Oncology Group performance status $\leq$2; (*vii*) adequate bone marrow function (white blood cell count $\geq$2,000/mm,^{3} platelet count $\geq$75,000/mm^3), renal function (serum creatinine level $\leq$2.0 mg/dL) and liver function (serum bilirubin level <2.0 mg/dL, both alanine aminotransferase and aspartate aminotransferase <100 IU/L) and (*viii*) provision of written informed consent. The exclusion criteria were as follows: (*i*) active malignancy other than early gastrointestinal cancer that was curable with endoscopic treatment within 1 year; (*ii*) systemic infection requiring antibiotics; (*iii*) significant cardiovascular disease (uncontrolled hypertension, myocardial infarction, unstable angina, congestive heart failure), uncontrolled diabetes mellitus, or liver cirrhosis; (*vi*) baseline stage T4 before CRT; (*v*) presence of lymph node or distant metastasis confirmed by computed tomography (CT) after CRT and (*vi*) known porphyria.

Evaluation of baseline clinical stage and the effect of CRT

Baseline clinical stage was determined using the TNM classification of the International Union Against Cancer.[13] Clinical T stage was evaluated by endoscopy, endoscopic ultrasound (EUS) and CT of the chest. Clinical N and M stages were evaluated by EUS and CT of the neck, chest and abdomen. In this study, lymph node metastasis was diagnosed clinically if the lymph node was $\geq$10 mm in diameter on CT. After completion of CRT, all patients were followed-up with both endoscopy and CT at 1, 3, 6, 9 and 12 months, and then every 4 months after completing CRT.

Evaluation of the local failure at the primary site after CRT

Before PDT, the depth of all failure lesions was evaluated using EUS (EU-M2000, Olympus Co. Ltd., Tokyo, Japan). We carefully observed the lesions with a high-frequency (20 MHz) miniature probe. When we detected a hetero-echoic solid component in the submucosal layer, we diagnosed it as a local failure lesion.

PDT treatment and surveillance

All PDTs were performed as inpatient procedures. PDT began with intravenous administration of 2 mg/kg of porfimer sodium (Photofrin, Pfizer Japan Inc.) followed by excimer dye laser irradiation. Porfimer sodium was reconstituted as a 2.5 mg/mL solution in 5% glucose. It was injected within 5 min, and the injection rate was less than 12 mL/min. A 630 nm wavelength laser beam was emitted by an excimer dye laser (EDL-1, Hamamatsu Photonics, Hamamatsu, Japan), and the laser light was delivered *via* a microlens- tip fiber, without any balloon or light diffuser, through the operative channel of the scope. An attachment was fitted to the tip of the scope to keep it facing the lesion and to maintain the distance between the tip of microlens fiber and the surface of the lesion during the procedure. The laser treatment was performed 48 hr after the injection of porfimer sodium. The fluence was 75 J/cm^2, with a fluence rate of 160 mW/cm^2 (4 mJ/pulse, 40 Hz pulse frequency). If the lesions were larger than 1 cm^2, multiple treatment fields were overlapped to cover the entire lesion. If the effect (*e.g.*, ischemic change of mucosa) after the laser treatment change, as evaluated by endoscopic observation was insufficient, additional laser irradiation was performed at a second session, 72 hr after the injection.[8,14,15]

All patients were instructed to avoid direct exposure to sunlight for 1 month after the injection of porfimer sodium to protect them from the adverse effects of skin photosensitization. Patients were discharged 2 weeks after laser irradiation, if there were no complications related to PDT. Adverse events were identified through a physical examination and endoscopic evaluation performed every 2 weeks until 2 months after PDT. One month after PDT, patients were assessed through a physical examination, measurement of haematological and biochemical variables in blood and endoscopic examination. The endoscopic examination with biopsy was repeated at least every month thereafter to evaluate the response and luminal toxicity of PDT until the response was confirmed. CT was used to evaluate distant organ or lymph node metastasis every 3 months for the first 2 years and every 6 months thereafter.

Statistical analysis

The primary endpoint of this study was the CR rate with salvage PDT. The sample size was determined assuming a binomial distribution. A threshold CR rate was considered to be 30%, and a CR rate of 60% was considered to be of potential interest. The planned accrual was calculated as 25 patients