Chapter 9

Definitive Chemo-Radiotherapy for Resectable Esophageal Cancer — Unresolved Problems Remain

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1. Introduction

Esophageal cancer, the 8th most common cancer and 6th leading cause of cancer deaths worldwide (Jemal et al., 2010), remains an invasive disease with 5-year overall survival rates (SRs) of only 20% in the USA (Daly, et al., 1996), 13% in UK (http://info.cancerresearchuk.org/cancerstats/types/oesophagus/survival/), and less than 10% in most parts of Europe (Keighley 2003). In Japan, an updated nationwide survey (http://ganjoho.jp/public/statistics/backnumber/2011_en.html) has demonstrated 5-year SRs of 33% for all esophageal cancers and 43% for resected cases, while in the USA, the survivals have improved to 42% in the past decade (Rice et al., 2009). Still, these statistics consistently confirm that survival remains disappointing, with less than half of all patients surviving at 5 years. Where the disease appears resectable and patients are sufficiently fit, surgery remains the mainstay of curative therapy. However, the overall poor prognosis with esophagectomies has led to the investigation of multimodal therapies in order to improve the treatment results. Among these, preoperative chemo-radiotherapy (CRT) (neoadjuvant CRT) has been developed and proved promising; nonetheless, morbidity and mortality have increased. What this means is that any improvement in survival rates of complete resection or local disease control by neoadjuvant CRT happens at the expense of greater toxicity. Several meta-analysis have elucidated that preoperative CRT significantly (Fiorica et al., 2004) or at least non-significantly increased (Kranzfelder et al., 2011; Urschel et al., 2003) postoperative in-hospital mortality.

On the other hand, evidence for CRT as a curative intent (definitive CRT: dCRT) has been established for patients with esophageal cancer who otherwise do not qualify for surgery due to disease extent and/or medical comorbidity. In Japan, dCRT for T4/M1(lymph) squamous cell cancer (SCC) achieved 1-, 2-, and 3-year SRs of 41%, 27-32%, and 22-23%, respectively, which compared well with SRs of T4 SCC undergoing resection (Ishida, et al., 2004; Japanese

Society of Esophageal Diseases, 2005; Y Nishimura et al., 2002; Ohtsu, et al., 1999; Kumekawa et al., 2006) [Table 1], although they were not a nonrandomized comparison. Subsequently, three pivotal RCTs demonstrated that survival results were similar between dCRT and neoadjuvant CRT followed by surgery or surgery only. A German trial revealed that dCRT with at least 65Gy for T3-4/N0-1/M0 SCC offered similar survival results with less likelihood of treatment-related mortality as compared with neoadjuvant CRT with 40Gy radiation (Stahl, et al., 2005). A French FFCD trial recruiting T3/N0-1/M0 SCC patients found no benefit of subsequent surgery following CRT for those responding to CRT (Bedenne et al., 2007). This study has established a rationale that the response to neoadjuvant CRT is a favorable prognostic sign which allows the selection of patients most likely to benefit from dCRT, thereby indicating the potential of dCRT for organ-sparing treatments. A CURE trial conducted in China compared T2-3/N1 SCC patients undergoing standard esophagectomy with those undergoing dCRT with 50-60Gy radiation and observed no survival differences between these two treatments (Chiu et al., 2005). Consequently, a very recent meta-analysis has also elucidated that there is no trend regarding differences in overall survival between surgery and dCRT (Pöttgen et al., 2012).

Author	Tumor stage	Radiation dose	Chemotherapy	Histology	Number of patients	Complete response rate	Median survival time (months)	Survival	Tretment-related death
Ohtsu, 1999	T4 and/or M1 lymph	60 Gy	Fluorouracil Cisplatin	SCC	54	33%	9	1YSR=41% 3YSR=23%	6.8%
Nishimura, 2002	T4 N0-1 M0-1	60 Gy	Fluorouracil Cisplatin	SCC	28	32%	stage III=12 stage IV=5	2YSR=27%	NA
Ishida, 2004 (JCOG9516)	T4 and/or M1 lymph	60 Gy	Fluorouracil Cisplatin	SCC	60	15%	10	2YSR=32%	1.7%
Kumekawa, 2006	T1-4 and M1lymph	60 Gy	Fluorouracil Cisplatin	SCC	81	42%	14	1YSR=62% 3YSR=22%	11.8%

YSR; year survival rate

Table 1. Treatment results of definitive chemo-radiotherapy for far advanced esophageal cancer in Japan.

Against these backgrounds and considering that surgery for esophageal cancer is a formidable procedure with significant morbidity and mortality (as discussed in section3.1) which raises concerns about its applicability in most patients, dCRT, at first investigated with palliative intent, has been further extended to resectable cases. While there was much initial enthusiasm for dCRT, notes of caution have been raised in interpreting the accumulated dCRT experience. These should be resolved for the further advancement of multimodal approaches for esophageal cancer. This chapter introduces current problems to be taken into account when performing dCRT, especially for patients with potentially resectable esophageal cancer.

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2. Definitive CRT for resectable esophageal cancer is promising and could be an alternative to esophagectomy

Many chemotherapeutic agents are potential candidates that could be combined with radiation (Kleinberg et al., 2007). Among these, the most frequently used agents are fluorouracil and cisplatin, both act as radiosensitizers. Fluorouracil inhibits DNA and RNA synthesis resulting in decreasing radiation-induced DNA injury repair, which eventually enhances radiation-induced cytotoxicity. Cisplatin forms inter- and intrastrand cross-links to DNA that impede repair. This action also leads to decrease in cellular repair in response to radiation-induced damage. Therefore, besides a direct action of fluorouracil and cisplatin to DNA, these two agents and radiation act synergistically.

Several nonrandomized comparisons have been conducted to investigate whether dCRT could achieve the same impact on survival as esophagectomy for those patients deemed suitable for surgery. More important are the encouraging results of dCRT for patients with operable rather than inoperable esophageal cancer. Table 2 lists the results of dCRT for each stage of esophageal cancer; these studies of dCRT with at least 60Gy radiation have shown consistent favorable SRs, which compare favorably with the Japan nationwide 3-year SR (44%) of surgery only (Japanese Society of Esophageal diseases, 2005). Ishikura et al. (Ishikura, et al., 2003) and Hironaka et al. (Hironaka et al., 2003) respectively recruited T1-3 (70% T3) and T2-3 SCC patients, and dCRT yielded 3-year and 5-year SRs of 49-55% and 46-49%, respectively. Three other dCRT studies revealed promising 3-year SRs which were 80% for patients with stage II SCC (Morota et al., 2009), 45% for those with stage II and III SCC (K Kato et al., 2011), and 72% for those with stage 0-III SCC (Murakami et al., 1998). These results motivated the researchers to conduct dCRT studies for less progressed esophageal SCC. For T1N0M0 stage I esophageal SCC, dCRT resulted in 1-, 2-, 3-, 4-, and 5-year SRs of 98%, 93%, 79-89%, 81%, and 66-67%, respectively, which could be compared favorably with survivals of surgical cases (H Kato et al., 2009; Minashi et al., 2006; K Yamada et al., 2006; Yamamoto et al., 2011). These findings are indeed encouraging and dCRT could be an alternative to esophagectomy. In addition, since dCRT can preserve the esophagus, it could theoretically offer better posttreatment quality of life than that for patients treated by surgery. Indeed, esophagectomy resulted in worse functional, symptomatic, and global quality of life scores at 6 weeks postoperatively than before surgery (Blazeby et al., 2000). However, the recently accumulated data on dCRT has raised several issues of concern.

3. Problems remain to be resolved

3.1. Invasiveness of dCRT

When considering dCRT—especially for potentially resectable esophageal cancer, risks from the treatment, i.e., treatment-related complications or death, should be taken into account in evaluating whether dCRT could substitute for surgery. Some patients undergoing dCRT have experienced severe grade 3/4 pericarditis, pleural effusion, and radiation pneumonitis, which

Author	Tumor stage	Radiation dose	Chemotherapy	Histology	Number of patients	Complete responders (%)	Median survival time (months)	Survival
Advanced cancer								
Hironaka, 2003	T2-3 N any M0	60Gy	Fluorouracil Cisplatin	SCC	53	37(70%)	33	3YSR=49% 5YSR=46%
Ishikura, 2003	T1-3,M0 (70% T3)	60Gy	Fluorouracil Cisplatin	SCC	67	ND	44	3YSR=55% 5YSR=49%
Kato, 2011 (JCOG9906)	II and III	60Gy	Fluorouracil Cisplatin	SCC	76	46(62%)	29	3YSR=45% 5YSR=37%
Morota, 2009	I-IVB	60Gy	Fluorouracil Cisplatin	SCC	69	36(52.2%)	ND	stage I 3YSR=80% stage II 3YSR=80% stage III 3YSR=30% stage IV 3YSR=30%
Murakami, 1998	0-III	60-75Gy	Fluorouracil Cisplatin	SCC	30	16(53.3%)	not reached	2YSR=81% 3YSR=72%
T1 cancer								
Kato, 2009 (JCOG9708)	T1N0M0	30Gy	Fluorouracil Cisplatin	SCC	72	63(88%)	not reached	2YSR=93% 4YSR=81%
Minashi, 2006	T1N0M0	60Gy	Fluorouracil Cisplatin	SCC	41	36(88%)	not reached	1YSR=98% 3YSR=79% 5YSR=67%
Yamada, 2006	T1N0M0	55-66Gy	Fluorouracil Cisplatin	SCC	63	ND	ND	5YSR=66%
Yamamoto, 2011	T1N0M0	60Gy	Fluorouracil Cisplatin	SCC	54	ND	not reached	1YSR=98% 3YSR=89%

SCC; squamous cell cancer, YSR; year survival rate

ND; not described

Table 2. Treatment results of definitive chemo-radiotherapy for potentially resectable esophageal cancer.

respectively developed in 1.4-16% (Hironaka et al., 2003; Ishikura et al., 2003; K Kato et al., 2011; Kumekawa et al., 2006; Minashi et al., 2006; Morota et al., 2009; Sasamoto et al., 2007), 1.4-14% (Hironaka et al., 2003;, Ishihara et al., 2010; Ishikura et al., 2003; K Kato et al., 2011; Kumekawa et al., 2006; Li et al., 2010; Minashi et al., 2006; Morota et al., 2009; Sasamoto et al., 2007), and 1.2-14% (Hironaka et al., 2003;, Ishihara et al., 2010; Ishikura et al., 2003; K Kato et al., 2011; Kumekawa et al., 2006; Morota et al., 2009; Sai et al., 2004; Yamamoto et al., 2011; Yamashita et al., 2008) of the study population. These complications eventually caused

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treatment-related death at a rate of 3-14% of the study population (K Kato et al., 2011; Morota et al., 2009; Sai et al., 2004; Sasamoto et al., 2007; Yamashita et al., 2008) or 8-12% of the CR patients (Ishihara et al., 2010; Ishikura et al., 2003; Kumekawa et al., 2006; Minashi et al., 2006; Sasamoto et al., 2007) [Table 3]. Especially, 8% of treatment-related death among the CR patients with stage I disease (Minashi et al., 2006) cannot be overlooked because they would be expected to survive by surgery unless fatal complications occurred.

Author	Grade 3/4 Toxicities			Tretment-related death	
	Pericarditis	Pleural effusion	Pneumonitis	of all patients	of CR patients
Hironaka, 2003	10.8%*	13.5%*	8.1%*	0.0%	ND
Ishihara, 2010	NA	0.9%**	2.7%**	ND	8.2%
Ishikura, 2003	5.8%	5.8%	2.2%	ND	10.3%
Kato, 2011 (JCOG9906)	16.0%	9.0%	4.0%	5.3%	ND
Kumekawa, 2006	3.7%	3.7%	1.2%	ND	11.8%
Li , 2010	NA	6.8%	NA	ND	ND
Minashi, 2006	2.8%*	11.1%*	0.0%	ND	8.3%
Morota, 2009	1.4%	1.4%	1.4%	2.9%	ND
Sai, 2004	NA	NA	13.8%	13.8%	ND
Sasamoto, 2007	8.9%	8.9%	NA	7.1%	7.1%
Yamamoto, 2011	0.0%	0.0%	3.7%	ND	ND
Yamashita, 2008	NA	NA	6.1%	6.1%	ND

*among the complete responders, **death rate

ND; not described, CR; complete response

Table 3. Mortality and late morbidity of definitive chemo-radiotherapy.

The heart is susceptible to radiation injury. Pericardial damage is most frequently mentioned, but all structures of the heart are at risk. Mediastinal radiation causes inflammation and progressive fibrosis of all of the structures of this organ. A worsening of clinical severity with increased radiation volume has been suggested. The risk of pericarditis has been found to rise with increased total dose and larger dose per fraction, reaching 3-fold and 2-fold greater relative risks at total doses of 41 Gy or greater, or a dose per fraction of 3.0 Gy or greater, respectively (Cosset et al., 1991). Another study also demonstrated that larger fraction size has a significant relationship with the chance of pericarditis (Martel et al., 1998). These observations suggest that dose effect as well as fractionation effect account for the increased risk of pericarditis.

Radiation pneumonitis has been reported in patients who have undergone mediastinal radiation therapy for various diseases. The risks of radiation pneumonitis rise when radio-

therapy is combined with chemotherapy (McDonald et al., 1995; M Yamada et al., 1998). The risks of lung toxicity appear to be related to dose-volume parameters such as the irradiated lung volume, mean lung dose (Hernando et al., 2001), total dose (Roach et al., 1995), daily fraction dose (Roach et al., 1995), and number of daily fractions (Roach et al., 1995), —although there are some inconsistencies (Allen et al., 2003). Similarly, the percentage of lungs receiving a specified dose has also been reported to be a predictor of pneumonitis (Madani et al., 2007; Tsujino et al., 2003).

The obstruction of cardiac and mediastinal lymphatic vessels due to radiation fibrosis has been postulated as a possible etiology of radiation-induced pericardial and pleural effusions. As a result, radiation-induced cardiac or lung disease is responsible for a certain fraction of death not directly attributable to esophageal cancer itself in some patients who would survive if they could have undergone surgery without complications. Although nonsurgical approaches are appealing in trying to manage this difficult disease, it is a fact that there is a fine therapeutic window because of the significant toxicities, and the toxicity may outweigh any potential advantages.

If treatment-related morbidity and mortality of dCRT exceed those of surgery, the benefits of dCRT may be cancelled. Therefore, the risk balance between dCRT and surgery should be taken into account in consideration of dCRT; however, one should remember that the morbidity and mortality of esophagectomy differ considerably between countries. Surgical mortality was 2-4% in Japan (Fujita et al., 2010; Suzuki et al., 2011; Tachimori et al., 2009), while 4.2-7.6% in Taiwan (Lin et al., 2006), 6% in Italy (Ruol et al., 2009), 4-13% in the Netherlands (Steyerberg et al., 2006; Wouters et al., 2008), and 6-23% in the USA (Atkins et al., 2004; Bailey et al., 2003; Birkmeyer et al., 2002; Dimick et al., 2005; Finks et al., 2011; Rentz et al., 2003), suggesting that differences in surgical mortality between countries can be more than doubled or quadrupled.

However, the risk comparison between dCRT and surgery should require considerations of the hospital volume, surgeon volume, specialization, study period, and country, i.e., when and where the studies of dCRT are conducted, as well as the number of esphagectomies that each surgeon performs. With regard to hospital volume, even in the USA —where surgical mortality is generally high, hospital mortality after esophagectomy varied from 23% for institutions undertaking <2 cases per annum to 8% for those undertaking 20 or more cases per annum (Birkmeyer et al., 2002). In Japan, the average mortality was 1.8% when >51 esophagectomies per annum were undertaken, compared with 4.6% if 20 or fewer esophagectomies were performed per annum (Suzuki et al., 2011). Fujita et al. (Fujita et al., 2010) and Kazui et al. (Kazui et al., 2007) also reported a larger hospital volume with a lower 30-day or in-hospital mortality rates. The same volume-outcome relationship was also observed in Taiwan (Lin et al., 2006) and the Netherlands (Wouters et al., 2008). In addition, high volume surgeons experienced a 4.2% mortality rate, which was one-quarter of that of low volume surgeons, approaching the average in-hospital mortality in Japan (Migliore et al., 2007). Also in Japan, risk of morbidity by low volume surgeons is twice that of high volume surgeons (Yasunaga et al., 2009). Collectively, a larger experience of esophagectomies could significantly reduce the 30-day or in-hospital mortality from 18% to 5% (Metzger et al., 2004).

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The study period is also a determinant. Single institutions in the USA (Orringer et al., 2007) or Italy (Ruol et al., 2009) experienced consistently decreased hospital mortality from 4% to 1% (Orringer et al., 2007) or from 8.2% to 2.6% (Ruol et al., 2009). Taking into account the various determinants of hospital mortality, the treatment-related death rates of 8-12% among CR patients of dCRT are undoubtedly higher than those of surgical mortality in Japan, but equal to or lower than in some countries. Considering the balance between the risks of dCRT and those of surgery, dCRT is regarded as a risky treatment as compared with surgery in some countries or in some institutions where surgery can be performed more safely.

3.2. Response evaluation is not necessarily perfect

The lack of any definitive diagnostic methods currently available for the response evaluation after dCRT remain pressing issues following dCRT. Strikingly, some segments of patients who underwent surgery following dCRT due to persistent disease proved to be complete responders postoperatively. The rates of such seemingly unnecessary salvage surgery are 10-50% (Ariga, et al., 2009; Beseth et al., 2000; Lim et al., 2003; Murakami et al., 1998; M Nishimura et al., 2007; Tachimori et al., 2009; Wilson et al., 2002). On the other hand, clinically diagnosed CR patients sometimes prove to have residual diseases and eventually exhibit relapse. The rates of overall recurrence or local recurrence after CR are substantial, being respectively 19-67% and 14-40% (Di Fiore et al., 2006; Ishihara et al., 2010; Kumekawa et al., 2006; Minashi et al., 2006; Morota et al., 2009; Murakami et al., 1998; Takeuchi et al., 2007; Tougeron et al., 2008; Wilson et al., 2000) [Table 4], suggesting that patients whose tumor response is deemed complete after dCRT could have residual diseases and that clinically CR is not always a reason to preclude further additional treatment. Such local recurrence rates do not depend on the initial tumor stage or depth. These discrepancies may be ascribed to the limitations of current imaging methods.

There are several diagnostic tools for evaluating responses to CRT. Endoscopy is an easily available means of investigation, but its accuracy is low as recurrent or residual tumors often lie beneath the mucosa [Figure 1]. Negative endoscopy findings have sometimes included microscopic foci of a residual tumor in the resected esophagus specimens. Moreover, the differentiation between tumor and radiation changes is not easy. A false negative rate of 48% for biopsy by endoscopy (Jones et al., 1997) suggests a poor correlation between endoscopic findings and pathologic status.

Endoscopic ultrasonography (EUS) also cannot reliably distinguish a residual tumor from postinflammatory changes, which is, on the other hand, a characteristic of the efficacy of dCRT. Even in earlier reports demonstrating the efficacy of EUS, (Hirata et al., 1997; Willis et al., 2002), it should be noted that a perfect discrimination between T0 and T1 tumors was not a consideration) since a certain degree of remaining tumor (<50-70%) was considered an EUS-based response, or a scattered or even a remaining degree of 1/3< viable cells was considered a pathological response. Such a cut-off value is less useful for deciding the need for salvage surgery following dCRT because only patients with no viable cells could theoretically be escaped from salvage surgery. EUS T staging accuracy after neoadjuvant CRT was only 43%,

Author	Tumor stage	Radiation dose	Histology	Number of patients	Complete responders (%)	Overall recurrence rate after CR	Local recurrence rate after CR
Di Fiore, 2006	T1-4/N0-1/M0	50 Gy or 60 Gy	SCC	116	86 (74.1%)	ND	40%
Ishihara, 2010	I-IVA	60 Gy	ND	173	110 (63.6%)	26%	12%
Kumekawa, 2006	T1-4 and M1lymph	60 Gy	SCC	81	34(42.0%)	ND	25%
Minashi, 2006	T1N0M0	60 Gy	SCC	41	36(88%)	39%	14%
Morota, 2009	I-IVB	60 Gy	SCC	69	36(52.2%)	ND	17%
Murakami, 1998	0-III	60-75 Gy	SCC	30	16(53.3%)	19%	ND
Takeuchi, 2007	II-III	60 Gy	SCC	178	113 (63.5%)	36%	ND
Tougeron, 2008	I-IV	50-55 Gy	SCC+ADC	109	63(58%)	52%	33%
Wilson, 2000	anyT, anyN, M0	50 Gy	SCC+ADC	31	24 (77.4%)	67%	21%

SCC; squamous cell cancer. ADC; adenocarcinoma

ND; not described, CR; complete response

Table 4. Overall and local recurrence rates among CR patients undergoing dCRT.

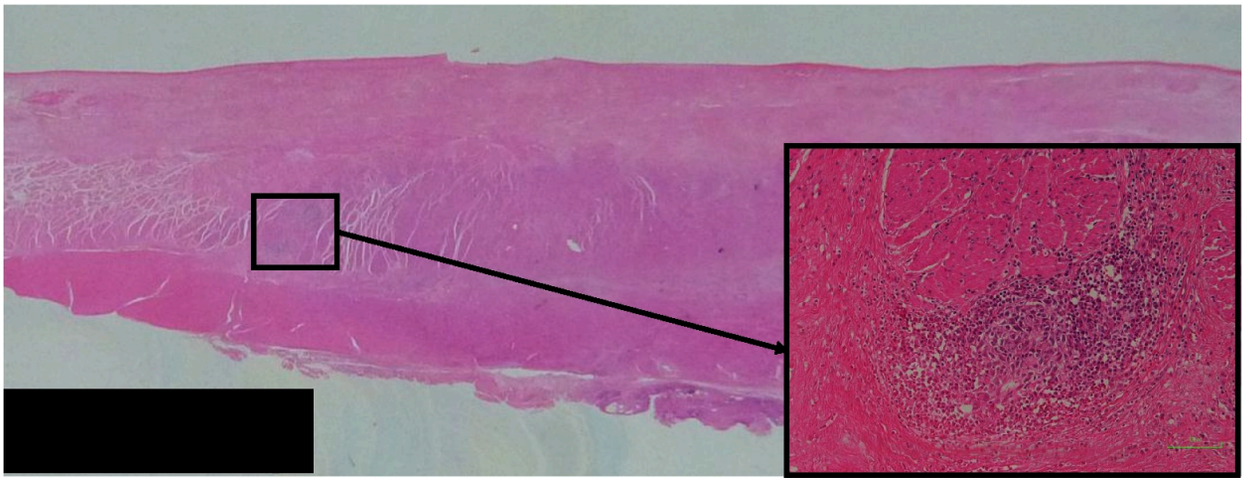

Figure 1. Low and high magnifications of a patient who was considered CR after CRT. Histological specimens revealed small foci of a residual tumor in the esophageal wall which could not be detected by endoscopically obtained biopsy specimens preoperatively.

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a rate ascribed to significant fibrosis and inflammation caused by CRT (Isenberg et al., 1998). Consequently, EUS had a tendency to overstage lower pathological T stages. On the other hand, 79% of pathologically complete responders were diagnosed as having T+ disease (Zuccaro et al., 1999). These T+ patients underwent immediate post CRT surgery, but this could deem unnecessary because of pathological CR. Similarly, EUS could not detect microscopic disease, while 27% of patients with positive EUS findings proved to have no residual tumor in the resected specimens (Beseth et al., 2000). Furthermore, EUS may be suboptimal when the sonography probe cannot pass the tumor.

Researchers have reported a low accuracy of CT for the assessment of responses in patients with esophageal cancer; this accuracy was substantially worse than that of EUS and FDG-PET (fluorine18-labelled deoxyglucose in positron emission tomography). This is most likely owing to the difficulty in the differentiation between viable tumors and reactive changes, including edema, fibrosis, and inflammation at CT. CT tumor volume change was poorly correlated with pathological tumor response (Griffith et al., 1999). Some tumors exhibited marked volume regression with a poor histological response, while some tumors showed little volume regression with a considerable histological response. This means that CT by itself represents an inadequate tool in assessing those who have residual disease and those who should undergo surgery following CRT. Jones et al. reported the same results (Jones, et al., 1999).

On the other hand, PET is a useful noninvasive tool in discriminating responders from nonresponders, with the colleration between PET-based response assessment and pathology being 78% (Flamen et al., 2002). The sensitivity and specificity of PET ranged from 71-100% and 55-95%, respectively (Brücher et al., 2001; Flamen et a., 2002; Weber et al., 2001). Any false positive results are attributable to the metabolically active leukocytes or macrophages associated with post CRT inflammation. False negative phenomena can occur because PET is unable to detect perfectly the residual viable disease in the primary tumor.

3.3. Salvage surgery is highly invasive

Patients who have received dCRT should undergo subsequent surgery if the tumors exhibit strictures or subsequent relapse. Salvage surgery is a surgery for residual or recurrent disease following dCRT, but it is technically more difficult and highly invasive than primary surgery, leading to increased morbidity (50-79%) and in-hospital mortality (7-22%) due to the adverse events of predominantly respiratory complications and anastomotic leakage (Chao et al., 2009; Nakamura et al., 2004; M. Nishimura et al., 2007; Oki et al., 2007; Smithers et al., 2007; Swisher et al., 2002; Tachimori et al., 2009; Tomimaru et al., 2006). These complications are attributable to the radiation-induced injury in the thoracic cavity that causes an increase in bleeding, fibrotic masses around the tumor due to the fibrogenic pathway that makes surgical technique more difficult, and an increasingly fragile stomach, esophagus, and trachea arising from the impaired blood supply that eventually causes anastomotic leakage or conduit necrosis. Even in Japan, these hospital mortality rates are obviously higher than those for primary esophagectomy reported from specialized centers or in a nationwide survey (2-4%) (Fujita et al., 2010; Suzuki et al., 2011; Tachimori et al., 2009). Reserving surgery for patients not already cured by CRT should always be taken into account in performing dCRT, and efforts

should be continuously made to reduce mortality and to select patients who stand to benefit most from this invasive treatment.

First, invasiveness undoubtedly depends on surgical procedure. The most common surgical approaches which are applicable to cancers of the upper, middle and lower esophagus are the Ivor-Lewis or McKeown esophagectomy. The Ivor-Lewis esophagectomy involves right thoracotomy with midline laparotomy and an anastomosis of the gastric conduit to the proximal mediastinal esophagus (at or above the azygos vein). The McKeown technique involves right thoracotomy, laparotomy, and cervical anastomosis, which facilitates precise surgical staging and enables more local control (van de Ven et al., 1999). The extent of lymphadenectomy is three-field (cervial thoracic, abdominal), which has traditionally been more prevalent in Japan, measuring the prevalence of positive cervical nodes (Akiyama et al., 1994; Nishihira et al., 1995). The survival benefit of three-field lymphadenectomy was suggeted in Japanese (Nishihira et al., 1998) and Western series (Altorki et al., 2002). Importantly, the risks of positive cervical nodes are substantial even at an earlier stage (Stein et al., 2005), and are seemingly independent of histological types (SCC or adenocarcinoma) or independent of tumor location within the esophagus (Akiyama et al., 1994; van de Ven et al., 1999). The McKeown technique enables this dissection to be performed under direct vision, allowing more precise dissection in cases where the tumor is large, lymphadenopathy is present, or the tumor is located in proximity to the airway (upper or middle thoracic esophagus). However, in salvage surgery, attempts have been made to reduce surgical morbidity and mortality with preservation of the blood supply to the trachea or to the main bronchus as well as to the reconstruction conduit. These include a reduced scope of lymphadenectomy with avoidance of cervical lymph node dissection or the preservation of right and left bronchial arteries (Tachimori et al., 2009).

Second, an accurate prediction of resection status prior to surgery is important at the time of completion of dCRT since resection status is one of the significant factors that affect survival after salvage surgery. Long term survivors after salvage surgery were those undergoing R0 resection, while no patients left with gross or microscopic residual tumors after salvage surgery (R1/R2 resections) survived more than 24 months in any series (Chao et al., 2009; Nakamura et al., 2004; Oki et al., 2007; Swisher et al., 2002; Tachimori et al., 2009; Tomimaru et al., 2006). Multivariate analysis also confirmed resection status correlation with patient survival (Chao et al., 2009; Tomimaru et al., 2006). However, the resection status cannot be confidently predicted before surgery or even during surgery because of the indistinct planes between a tumor and fibrotic masses within the irradiated mediastinum. In this regard, PET, which has a relatively high specificity, could identify non-responders for dCRT and may be a more useful imaging modality than CT or EUS (Swisher et al., 2004) to select patients who are absolutely unfit for salvage surgery, allowing for early modifications of the treatment strategy of such selected patients.

Third, it is imaginable that larger, more advanced cancers are more difficult to control than smaller ones and require longer doses of RT; however, higher radiation doses are associated with increased morbidity. A dose of 60Gy of radiation has been used for dCRT in Japan (Kenjo et al., 2009). In this regard, the possibility of reducing total radiation volume from 64.8Gy to

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50.4Gy (Minsky et al., 2002; Nakajima et al., 2009) has recently prompted a phase II study of dCRT with a radiation dose of 50.4Gy for stage II/III esophageal SCC (JCOG0909).

4. Future perspectives

The combination of conventional CRT with molecular targeting therapies has been developing. This combination is encouraged by the findings that radiotherapy plus cetuximab, a monoclonal antibody against epidermal growth factor receptor, for loco-regionally advanced SCC of the head and neck resulted in the prolonged duration of loco-regional control, progression free survival, and overall survival as compared with radiotherapy alone (Bonner et al., 2006; Bonner et al., 2010). The feasibility of adding cetuximab to CRT for esophageal cancer is supported by the safety profiles of this combination without any increase in esophagitis or other radiation-enhanced toxicity (Safran et al., 2008). The ongoing phase III trials (NCT 00655876, NCT01107639, NCT00509561) will provide evidence whether cetuximab in combination with CRT is effective in locally advanced or resectable esophageal cancer (http://clinicaltrials.gov).

A gain in survival with a substantial increase in toxicity necessitates considerable caution that immediately draws the attention of clinicians. Diagnostic tools which can accurately evaluate tumor response early in the course of dCRT can facilitate decisions about whether this toxic therapy should be continued in responders, or stopped in non-responders. However, there are currently no modalities that can definitively confirm CR. The reason for this problem is that the tools to estimate individual patient prognosis or tumor response are unreliable, and a diagnosis of CR is possibly merely by resected specimens. This means that negative findings by these imaging methods do not rule out residual disease. Clearly, patients with residual disease would no longer be long term survivors without undergoing resection. Therefore, efforts should continue to establish diagnostic tools for the detection of residual diseases after CRT.

One challenge in this regard lies in the detection of histologic markers—such as p53, Ki67, and EGF-R—for the prediction of therapeutic response; however, neither a single marker nor a combination of markers can correctly be used to predict the response with sufficient accuracy. The small number of patients or small number of genes investigated in this field is a further limitation. In the future, gene profiling may help identify markers that can be used in combination with conventional imaging methods for the prediction of the response to dCRT.

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