

Postoperative Radiotherapy for Thoracic Esophageal Carcinoma with Upfront R0 Esophagectomy

This article was published in the following Dove Press journal:
Cancer Management and Research

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Abstract: Multidisciplinary therapies can improve the survival of patients with locally advanced esophageal carcinoma. However, the determination of the optimal modality is still a controversial subject. Many randomized controlled trials in the late 20th century showed that there was no survival benefit when postoperative radiotherapy was added to surgery for esophageal carcinoma. As a result, the treatment modality shifted thereafter to neoadjuvant therapies. Even so, these trials are criticized for many limitations and an increasing number of studies (mainly nonrandomized controlled trials) has indicated that postoperative radiotherapy/chemoradiotherapy can improve the survival of patients with a poor prognosis after R0 esophagectomy. Additionally, a large number of patients with locally advanced esophageal carcinoma still choose upfront surgery in the clinical practice due to many reasons. Therefore, postoperative radiotherapy seems to be a feasible treatment for these patients with a poor prognosis, particularly in the new era of conformal radiotherapy. Here, we review published studies on postoperative radiotherapy/chemoradiotherapy, and we discuss the clinical issues related to postoperative radiotherapy, such as the indication, target volume, total radiation dosage, time interval and complications of postoperative radiotherapy with or without chemotherapy, to make recommendations of postoperative radiotherapy for both current practice and future research in esophageal carcinoma.

Keywords: esophageal neoplasm, postoperative radiotherapy, survival, clinical target volume

Introduction

Esophageal carcinoma (EC) is the sixth most common cause of cancer-related death worldwide and contributes to a major global health burden.¹ Surgery is the cornerstone of treatment for resectable EC; unfortunately, survival is very poor for patients who undergo surgery alone (SA).² To improve survival, multidisciplinary therapies have been studied worldwide. Due to the unsuccessful or even poor results in the trials of the late 20th century,^{3–7} postoperative radiotherapy (PORT) is therefore not recommended for patients with negative margin diseases after esophagectomy and the multidisciplinary approach shifts to neoadjuvant therapies.² However, surgery is still the first choice for a large number of patients due to many reasons in the real world, particularly in many underdeveloped or developing countries.^{8,9} Both locoregional recurrence and distant organ metastasis represent common treatment failures for patients with SA.^{10–13} Therefore, in the opinion of most physicians, upfront SA is

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thought to be insufficient for diseased patients who have a poor prognosis (such as pT3/4 or pN+). Despite the lack of more randomized controlled trials (RCTs), many published studies have suggested that postoperative radiotherapy/chemoradiotherapy can improve survival in many patients with locally advanced EC.^{14–16}

PORT has the advantage of providing reasonable treatment according to the accurate pathological stage. On the one hand, many patients with inaccurately staged early EC can avoid overtreatment, and on the other hand, PORT can be chosen for many clinical early-stage EC cases with pathological upstaged diseases. Moreover, the pathological results provide an important clue for the design of the target volume, which may be a feasible method of individualized PORT. However, there is little consensus on the optimal populations, target volume, dosage, time interval and combined approach for PORT of EC. The aim of this paper is to review previous studies, to detail the clinical issues and to make recommendations of PORT for both current practice and future EC research.

Literature Review

Identification of Studies

Electronic databases, including PubMed, Scopus, EMBASE, Web of Science, and the Cochrane Library were searched for relevant studies until June 2020. The following key words were searched: (“esophageal” OR “oesophageal” OR “esophagus” OR “oesophagus”) AND (“cancer” OR “carcinoma” OR “tumor” OR “neoplasm”) AND (“adjuvant” OR “postoperative” OR “post” OR “perioperative” OR “peri”) AND (“radiotherapy” OR “chemoradiotherapy”). All the retrieved studies were screened in Endnote X8.1. The reference lists of the included studies, meta-analyses and systematic reviews were also manually searched to identify any eligible studies that reported the efficacy of surgery followed by radiotherapy (S+RT) or chemoradiotherapy (S+CRT).

S+RT or S+CRT versus SA

Eight RCTs compared the survival differences between S+RT and SA for EC.^{3–7,17–19} As shown in Table 1, five RCTs were conducted in the late 20th century^{3–7} and five RCTs were conducted in China.^{5,6,17–19} All patients in these studies had esophageal squamous cell carcinoma (ESCC) except one study that enrolled patients with cardia adenocarcinoma.⁵ The 100% R0 resection rate was recorded in four studies^{4,17–19} and two studies included patients with positive M1a nodes.^{4,7} There was no survival difference

between S+RT and SA in six studies.^{3,4,6,7,17,19} In one study, the S+RT group had poor survival compared to the SA group ($P<0.05$).⁶ Wang and colleagues found that S+RT improved not only disease-free survival (DFS) (34.9% vs. 11.3%, $P<0.001$) but also 5-year overall survival (OS) (48.1% vs. 30.2%, $P=0.007$) compared to SA in pT2N0M0 ESCC patients with high Ku80 expression.¹⁸ Although there was no OS difference in the study of Xiao and colleagues, subgroup analysis showed that S+RT can improve the 5-year OS from 13.1% to 35.1% for patients with stage III ESCC ($P=0.027$) and from 14.7% to 29.2% for patients with positive lymph nodes ($P=0.0698$).¹⁷ In the latest RCT, S+RT improved the 3-year DFS from 58.7% to 75.1% ($P=0.03$) and decreased the locoregional recurrence rate from 32.5% to 10.0% ($P=0.001$) in patients with pT2–3N0M0 ESCC.¹⁹

Only one RCT compared the survival differences between S+CRT and SA for stage II–III ESCC¹⁵ (Table 1). In this study, 78 patients were in the S+CRT group and 80 patients were in the SA group. There were significant differences in the 3-, 5-, and 10-year DFS (61.1%, 37.2%, 17.8% vs. 49.3%, 25.9%, 6.2%, $P<0.05$) and in the 3-, 5-, and 10-year OS (62.8%, 42.3%, 24.4% vs. 51.3%, 33.8%, 12.5%, $P<0.05$). The local recurrence rates in the S+CRT group and the SA group were 14.1% and 35%, respectively ($P<0.05$). No significant differences were detected when comparing complications.

A large number of retrospective studies have suggested that S+RT or S+CRT can improve survival for patients with poor prognostic factors, such as node-positive disease, stage III/IV disease, large tumors, and advanced T stage.^{8,9,16,20–27} A meta-analysis based on four RCTs and eight non-RCTs suggested that PORT was promising in improving 3-year OS and reducing the locoregional recurrence rate.²⁸ Another meta-analysis based on thirteen published studies confirmed that S+CRT yielded a significant survival benefit and improved local-regional control with tolerable toxicity for EC.¹⁴

S+CRT versus S+RT

There was no RCT comparing the efficacy between S+CRT and S+RT. Five retrospective studies, including two in China, two in America and one in Japan, were found after a systematic search (Table 2). Of them, four studies confirmed that S+CRT can improve survival compared with S+RT.^{8,24,29,30} The Japanese study showed that there was no survival difference between S+CRT and S+RT. However, this study was criticized for a low sample size (only 19 patients in each group).³¹

Table I RCTs Compared S+RT/S+RCT with SA for EC

First Author (Year)	Data Period	Country	Stage	Location	R0 Rate (%)	SCC (%)	Group	Number	OS	P value
Kunath ³ (1984)	1977–1983	German	I-III*	TEC	N	100	S+RT	13	15.5 m (mOS)	>0.05
							SA	10	9.2 m (mOS)	
Ténière ⁴ (1991)	1979–1985	France	No distant metastasis	Middle and lower TEC	100	100	S+RT	102	21% (5-year)	>0.05
							SA	119	19% (5-year)	
Fok ⁵ (1993)	1986–1989	China	No distant metastasis	TEC, cardia	46	80	S+RT	65	8.7 m (mOS)	0.02
							SA	65	15.2 m (mOS)	
Fok ⁶ & (1994)	1968–1981	China	N	Middle TEC	N	100	S+RT	42	10% (5-year)	>0.05
							SA	39	16% (5-year)	
Zieren ⁷ (1995)	1988–1991	German	II-IV & (4th UICC)	TEC	100	100	S+RT	33	22% (3-year)	>0.05
							SA	35	20% (3-year)	
Xiao ¹⁷ (2003)	1986–1997	China	I-III (5th UICC)	TEC	100	100	S+RT	220	41% (5-year)	0.447
							SA	275	37% (5-year)	
Wang ¹⁸ (2015)	2004–2009	China	T2N0M0** (7th UICC)	Middle TEC	100	100	S+RT	106	48% (5-year)	0.007
							SA	106	30% (5-year)	
Wei ¹⁹ (2020)	2012–2018	China	T2-3N0M0 (7th UICC)	TEC	100	100	S+RT	80	89% (3-year)	0.527
							SA	77	81% (3-year)	
Lv ¹⁵ (2010)	1997–2004	China	II-III***	TEC	79	100	S+RCT	78	24% (10-year)	0.021
							SA	80	13% (10-year)	

Notes: & We cannot access the full text of this article; & Patients without distant metastasis; *The stage system was not recorded; **Patients with Ku80 overexpression; ***The stage was based on a computerized tomography staging criterion which can be found in this article.

Abbreviations: m, months; mOS, median overall survival; N, not available; OS, overall survival; SA, surgery alone; SCC, squamous cell carcinoma; S+RCT, surgery followed by chemoradiotherapy; S+RT, surgery followed by radiotherapy; TEC, thoracic esophageal carcinoma; UICC, Union Internationale Against Cancer.

S+CRT versus Neoadjuvant Chemoradiotherapy Followed by Surgery (CRT+S)

Two prospective RCTs^{15,32} and six retrospective control studies^{33–38} compared S+CRT with CRT+S directly. Their characteristics are presented in Table 3. Most studies were conducted in Asian countries, including three in China,^{15,32,36} one in Taiwan³⁷ and one in Iran.³⁸ Most retrospective studies^{33–38} and published RCTs¹⁵ suggested that there were no significant differences in OS between CRT+S and S+CRT. However, most studies showed a trend toward survival benefits in the CRT+S group, except for one study.³⁸ Only one study showed significant survival benefits in the CRT+S group.³²

Controversies of Clinical Issues Indications

In the NCCN guidelines, surveillance is recommended for clinical T1-2N0M0 EC patients with negative margins (R0 resection) after radical surgery regardless of the pathological stage (p Any T, Any N) and CRT+S is recommended for patients with resectable clinical T3-4N0M0 or T1-4N+M0 diseases. However, there is no recommendation for patients with pathological T3-4N0M0 or T1-4N+M0 diseases who do not receive any preoperative therapies. It is assumed that upfront SA may not be insufficient for patients with poor prognostic factors. According to the results of Xiao's RCT¹⁷ and a large number of retrospective studies,^{8,20,22,24–27} PORT is associated with improved survival for patients with node-positive disease. Therefore,

Table 2 Retrospective Studies Compared S+CRT with S+RT for EC

First Author (Year)	Data Period	Country	Stage	Pathological Type (%)	Group	Number	OS	P value
Mukaida ³¹ (1998)	1990–1993	Japan	IIa–IV*	SCC (N)	S+CRT	19	25.2% (5-year)	>0.05
					S+RT	19	18.9% (5-year)	
Liu ²⁹ (2005)	1999–2002	China	T3-4N0-1M0 (6th AJCC)	SCC (100)	S+CRT	30	70.0% (3-year)	0.003
					S+RT	30	33.7% (3-year)	
Chen ²⁴ (2013)	2002–2008	America	T1-4N+M0 (7th AJCC)	SCC (100%)	S+CRT	164	47.4% (5-year)	0.03
					S+RT	140	38.6% (5-year)	
Wong ⁸ (2017)	1998–2011	America	T3-4N0-1M0, T1-4N1-3M0**	SCC (23.3%)	S+CRT	1036	46.3% (3-year)	0.001
					S+RT	117	31.3% (3-year)	
Zou ³⁰ (2020)	2007–2016	China	II–III (7th AJCC)	SCC (100%)	S+CRT	148	76.0% (3-year)	0.001
					S+RT	124	39.0% (3-year)	

Notes: *Patients without distant metastasis; **The stage system was not recorded.

Abbreviations: AJCC, American Joint Committee on Cancer; N, not available; OS, overall survival; SCC, squamous cell carcinoma; S+RT, surgery followed by radiotherapy.

in the latest Guideline of the Chinese Society of Clinical Oncology (CSCO), it is suggested that S+RT or S+CRT may be chosen for patients with node-positive disease in the annotations. Although there was no recommendation in all guidelines, PORT can also improve the survival of patients with stage III EC according to the results of Xiao's RCT¹⁷ and many retrospective studies.^{9,16,20,39} For patients with pT3N0M0 EC, adjuvant conformal radiotherapy may also be associated with improved survival.²³ Although CRT+S is now recommended for resectable locally advanced EC, there are few RCTs comparing CRT+S and S+CRT directly and most studies showed that there was no survival difference (Table 3). The optimal timing of chemoradiation combined with surgery will continue to be debated. To these points, S+RT or S+CRT should also be considered for EC, particularly clinical early-stage EC with pathological upstaged diseases and locally advanced EC without preoperative therapies. However, more multicenter RCTs are needed to confirm these findings.

Combination with Chemotherapy

There is a high occurrence of distant organ metastasis for EC. In the CROSS trial, blood metastasis occurred in 47.8% of patients with SA,¹² which was similar to finding in other studies.^{10,13} Chemotherapy can not only decrease distant recurrence but also be a radiotherapy sensitizer when concurrent chemoradiotherapy is used. Therefore, it should be another important part of multimodality therapy

for EC. The RTOG 85–01 trial confirmed that combined chemotherapy and radiotherapy increased the survival of patients with T1-3N0-1M0 ESCC compared with radiotherapy alone⁴⁰ and chemotherapy or chemoradiotherapy is recommended as the standard neoadjuvant treatment for locally advanced EC.² For adjuvant therapies, the combination of chemotherapy and radiotherapy can also improve survival compared with adjuvant radiotherapy alone according to many retrospective studies^{8,24,29,30} (Table 2) and a meta-analysis.⁴¹ Above all, the addition of chemotherapy should provide better survival than adjuvant radiotherapy alone.

In EC, neoadjuvant or definitive concurrent chemoradiotherapy is recommended.^{42,43} However, it remains unclear whether concurrent chemoradiotherapy or sequential setting is more beneficial for postoperative treatment. Wang AT and colleagues analyzed 4893 patients in the National Cancer Data Base (NCDB) from 1998 to 2011 and found that postoperative chemoradiation (either sequentially or concomitantly) after surgery was associated with improved OS for patients with node-positive disease or positive margins, and sequential setting was associated with the best survival ($P<0.001$).⁸ The presumable reason may be the lower toxicity in the sequential group due to the poor performance status after esophagectomy. Similar results were found in the adjuvant therapies for locally advanced or incompletely resected non-small-cell lung cancer.⁴⁴ However, the concurrent chemoradiotherapy group was associated with improved 1-year,

Table 3 Studies Compared S+CRT with CRT+S for EC

Author (Year)	Country (Region)	Data Period	Stage	Group	Number	SCC (%)	OS	P value
Malaisrie ³³ (2004)	Ill (Maywood)	1990–2001	II-III (5th AJCC)	CRT+S	27	22	45% (3-year)	0.15
				S+CRT	25	12	22% (3-year)	
Lv ¹⁵ (2010)	China (Nanjing)	1997–2004	II-III*	CRT+S	80	100	25% (10-year)	0.498
				S+CRT	78	100	24% (10-year)	
Davis ³⁴ (2011)	US (California)	1990–2001	Locally advanced EC	CRT+S	31	N	26% (5-year)	0.755
				S+CRT	27	N	22% (5-year)	
Hong ³⁵ (2013)	US (Stanford)	1995–2002	T3+NxM0, TxN+M0 **	CRT+S	126	31	37 months (mOS)	0.06
				S+CRT	40	28	17 months (mOS)	
Chen ³⁶ (2017)	China (Henan)	2006–2013	II-III (7th UICC)	CRT+S	49	100	48% (5-year)	0.091
				S+CRT	73	100	30% (5-year)	
Hsu ³⁷ (2017)	Taiwan (Taipei)	2008–2013	II-III (ICD-O-3)	CRT+S	286	100	44% (5-year)	0.315
				S+CRT	286	100	38% (5-year)	
Sadrizadeh ³⁸ (2018)	Iran (Masshad)	2006–2016	I-IV***	CRT+S	90	83	12 months (mOS)	0.69
				S+CRT	234	82	27 months (mOS)	
Xu ³² (2018)	China (Zhejiang)	2011–2015	II-III***	CRT+S	74	100	64% (3-year)	0.044
				S+CRT	75	100	49% (3-year)	

Notes: *The stage was based on a computerized tomography staging criterion which can be found in this article; **Patients without metastatic disease, positive M1a nodes; ***The stage system was not recorded.

Abbreviations: AJCC, American Joint Committee on Cancer; CRT+S, chemoradiotherapy followed by surgery; EC, esophageal carcinoma; ICD-O, International Classification of Diseases for Oncology; mOS, median overall survival; N, not available; OS, overall survival; S+CRT, surgery followed by chemoradiotherapy.

3-year and 5-year OS tolerable toxicity compared to the nonconcurrent chemoradiotherapy group in a meta-analysis.¹⁴ Therefore, more studies should be conducted to identify the optimal sequencing of the addition of chemotherapy.

Target Volume

Due to the complex lymphatic drainage system,⁴⁵ it is always challenging to design an appropriate target volume for preoperative, postoperative, or definitive radiotherapy in EC. Many target volumes have been used in past decades for PORT of EC, including: (1) a 3 to 5 cm margin at both the cephalad and caudal ends and a 1 to 2 cm margin around the initial tumor;^{5,46} (2) the supraclavicular areas and whole mediastinum with or without celiac areas (left gastric or/and paracardiac lymph nodes);^{4,15,17,47} (3) the supraclavicular areas and part of the mediastinum (from the cricothyroid membrane to 3 cm below the carina for proximal diseases and from the T1 vertebra to 3 cm below the primary tumor bed for middle and lower diseases);^{19,48} (4) a T-shaped field that includes only the bilateral

supraclavicular area, upper and middle mediastinum, and primary tumor bed (from the upper edge of the sixth cervical vertebra to 3 cm below the carina for proximal diseases to the lower edge of the primary gross tumor for middle and lower diseases);²⁴ (5) the bilateral supraclavicular areas and upper mediastinum;^{18,49} and (6) others.^{3,7,39} The irradiation fields of PORT used in the RCTs are shown in Table 4.

An appropriate target volume may not only decrease recurrence but also decrease radiotherapy-related complications. There are at least three important factors affecting the delineation of the lymph node target volume of PORT in EC. The first factor is the characteristics of the lymphatic drainage of the esophagus, which we reviewed elsewhere.⁴⁵ Because of direct drainage to many important extramural lymph nodes from submucosal vessels and bidirectional drainage, lymph node metastasis is frequently present in many important extramural lymph nodes in the lower neck, upper mediastinum, and perigastric areas for all thoracic ECs, even for early-stage diseases. As a result, lymph node metastasis of EC is fairly unpredictable,

Table 4 Methods of PORT in the RCTs

First Author (Year)	Irradiation Field	RT Technology	Dosage	Time Interval
Kunath ³ (1984)	Postoperative tumor bed, regions of lymph node metastasis, potential tumor lesion and regions of lymph node metastasis	2D-RT	50–55 Gy	N
Ténière ⁴ (1991)	The mediastinal, right and left supraclavicular areas and also to the celiac area when celiac lymph node invasion was present	2D-RT	45–55 Gy	Less than 3 months
Fok ⁵ (1993)	A 5 cm margin at both the cephalad and caudal ends of the initial tumor as shown by the preoperative barium swallow, with a cylindric diameter of 6 to 9mm. If the resection margin was positive, anastomosis should be included	2D-RT	49 Gy/14F (R0); 52.5 Gy/15F (not R0)	4–6 weeks
Zieren ⁷ (1995)	The first instance included the whole mediastinum and locoregional lymph nodes. Supraclavicular fossae were included for the upper TEC and the celiac area was included for the lower TEC. To shield the spinal cord, the irradiation fields were then reduced to the tumor bed with a cranial and caudal margin of 3 cm.	2D-RT	30.6 Gy/17F for first instance, and then to 55.8 Gy/31F	3–6 weeks
Xiao ¹⁷ (2003)	The bilateral supraclavicular areas (from the cricoid cartilage to 1.0 cm below the lower margin of the clavicles) and the entire mediastinum, the site of anastomosis, and the left epiploic and paracardiac lymphatics (T3-T12 or L1)	2D-RT	50 Gy/25F (supraclavicular areas); 60 Gy/30F (the midplane)	3–4 weeks
Wang ¹⁸ (2015)	The cervical, supraclavicular, and superior mediastinal regions (including the upper thoracic esophageal and tracheal regions)	3D-CRT	50–60 Gy and 2 Gy/day	One month
Wei ¹⁹ (2020)	From cricothyroid membrane to 3 cm below carina for proximal diseases and from T1 vertebra to 3 cm below tumor bed for middle and lower disease. Anastomosis was included when proximal tumor margin was less than 3 cm or proximal disease was observed	IMRT	50.4 Gy/28F for supraclavicular field and 56 Gy/28F for mediastinal field	Less than 3 months
Lv ¹⁵ (2010)	The anteroposterior fields of 30 patients including esophageal tumors and enlarged lymph nodes, with a 4–5 cm proximal and distal margin and a 1–2 cm radial margin. the anteroposterior fields of the following 48 patients were extended from the sixth cervical vertebrae to the first lumbar vertebrae, including the origin of esophagus and lymph drainage that encompassed the supraclavicular regions and left gastric lymph nodes. Dose boost was delivered through parallel opposed lateral or oblique portals	2D-RT	50 Gy and 2 Gy/day	4–6 weeks

Abbreviations: F, fractions; IMRT, intensity-modulated radiation therapy; N, not available; RT, radiotherapy; TEC, thoracic esophageal carcinoma; 2D-RT, two-dimensional radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy.

characterized by wide-range, bidirectional and skipping metastasis. The second factor is the surgical procedure. Two-field lymphadenectomy (2FL) or three-field lymphadenectomy (3FL) are both used in clinical practice. The standard 2FL consists of intrathoracic lymph node dissection from the subcarinal space down to the hiatus and upper abdominal lymph node dissection. Extended 2FL and 3FL may increase the chance of complete resection

of positive lymph nodes. However, regardless of whether 2FL or 3FL is used, the cervical, upper mediastinal and paraaortic lymph nodes are usually not resected or not completely resected because of the complex anatomical structures in these regions and the limitations of the surgery itself. The third factor is the recurrence pattern after upfront surgery. A large number of published studies have suggested that locoregional recurrence, particularly lymph

node recurrence in the cervical, upper mediastinal and paraaortic regions, is a common relapse after surgery.^{10–13,50–52} Above all, the cervical, upper mediastinal and paraaortic regions should be the major regions for PORT of thoracic EC.

Additionally, the tumor bed and anastomosis have been taken into consideration for PORT in various tumors.^{53,54} In fact, the tumor bed was commonly included in the target volume of PORT in previous studies in EC.^{3,5,7,15,19} However, according to many retrospective studies, the recurrence rate of the tumor bed is very low in patients with EC after radical surgery,⁵⁰ even in patients with pT3–4 stages.^{55,56} The recurrence rate of the anastomotic site is usually less than 5.0% (2.8–8.7%).^{10,12,57–59} To these points, these sites may not be necessary in the clinical target volume (CTV) of PORT for thoracic EC. However, the sites of recurrence can be affected by various factors, such as the tumor itself (TNM stage, histological subtype, differentiation, tumor location, region of positive lymph node, etc.), the operation method, the extent of lymphadenectomy, among others. Therefore, personalized target volume should be considered in clinical practice.

Total Radiation Dose (TRD)

As shown in Table 4, the TRD of PORT is 45 to 60 Gy and the single fractional dose is usually 1.8 or 2 Gy for EC in the RCTs. The determination of the optimal TRD for treating EC is still controversial. A retrospective study analyzed the effect of TRD on the outcome in patients with PORT for ESCC.⁴⁶ In this study, 54 patients were classified into two groups based on TRD delivery: the low group (less than 50 Gy) and the high group (at least 50 Gy). Although the high group was marginally significant for improved OS (hazard ratio (HR)=0.559, $P=0.066$), it was statistically significant for improved DFS (HR=0.398, $P=0.011$), and locoregional recurrence-free survival (HR=0.165, $P=0.001$) with acceptable complications. It has also been found that the 90% plus control point is 50 Gy for both squamous cell carcinomas of the upper respiratory and digestive tracts and adenocarcinomas of the breast.⁶⁰ Therefore, it is recommended that the TRD should be at least 50 Gy in PORT for EC. However, there is no RCT to confirm this result. Moreover, it is questionable whether the TRD should decrease when chemotherapy is added to PORT.

Time Interval After Surgery

PORT should start within 6 weeks after surgery; two RCTs specified within 3 months (Table 4). However, there is no direct evidence concerning the optimal time interval between surgery and PORT. Yamada S and colleagues found that there was no survival difference between patients with a waiting period of 30 to 39 days and patients with a waiting period of less than 30 days, and between patients with a waiting period of 40 to 49 days and patients with a waiting period of 50 or more days. However, the survival of patients with a waiting period of 30 to 39 days was significantly higher than that of patients with a waiting period of 40 to 49 days ($P<0.01$).⁶¹ Therefore, PORT should be started within 40 days after radical resection in this study. Another multicenter retrospective study also assessed the effect of PORT delay on survival for 316 patients.⁶² In this study, the waiting period after surgery varied from 12 days to over 60 days (median, 26 days). Patients with a particularly long waiting period (≥ 42 days) demonstrated a detrimental impact on OS ($P=0.021$) but not PFS ($P=0.580$). Therefore, it was recommended that PORT should be started within six weeks in this study. However, there is no RCT to confirm these results and it is also questionable whether the time interval can be prolonged when sequential chemotherapy is added before PORT.

Complications and Toxicities

Six of the nine RCTs reported complications or toxicity.^{5–7,15,17,19} In Fok's study,⁵ lesions in the intrathoracic stomach (gastritis, gastric ulcer, bleeding gastric ulcer, penetrating gastric ulcer and fistula to trachea) were found in 34 patients (37%) in the S+RT group and four patients in the SA group (6%) ($P<0.001$). The major reason should be that the substitute organ was placed either orthotopically or in the thoracic cavity within the target volume. Furthermore, the fractional radiation dose was 3.5 Gy which may lead to increased mortality in the S+RT group. As a result, the median OS was actually worse in the S+RT group (8.7 months vs 15.2 months, $P=0.02$). Additionally, 6 patients in both the S+RT group and the SA group had anastomotic strictures. In another study, respiratory symptoms in 25 patients, postoperative death in 3 patients and leaks in 11 patients were observed in the S+RT group (42 patients) while respiratory symptoms in 15 patients, postoperative death in 3 patients and leaks in 7 patients were observed in the SA group (39 patients).⁶ In

other RCTs,^{7,15,17,19} severe radiotherapy-related adverse events were not found in the S+RT group compared with the SA group. The commonly reported adverse events were anastomotic strictures, nausea, anorexia, weakness, leukopenia, anemia, and others.

The addition of chemotherapy to PORT may increase adverse events. Many studies have indicated that the incidence of grade 3 or more hematological toxicity,^{24,29,30} radiation esophagitis,²⁴ and gastrointestinal reactions^{24,30} was higher in the S+CRT group than in the S+R group, but patients could tolerate chemoradiotherapy. In a meta-analysis, it was found that the most common prevalent severe complications (grade 3–4) were leukocytopenia (0–36.8%), hypohemoglobinemia (0–16.7%), thrombocytopenia (0–10.5%), nausea/vomiting (0–18.4%), and stomatitis (0–5.3%) in the S+CRT group. However, S+CRT did not increase the risk of pneumonitis, anastomotic stenosis or severe hematologic toxicities compared to the S+RT group.¹⁴

Radiation-based adverse events can be affected by the performance status, the methods of surgery, the methods of radiotherapy (technology, irradiation field, and TRD), the combined therapy, etc. In the past, it was always thought that PORT is difficult for patients to endure after radical surgery, and radiotherapy is often not fully delivered. However, this idea is not in accordance with the results of published studies. Additionally, with the rapid development of operation methods, precise radiotherapy using optimal target volume and dosage, and new chemotherapy drugs with low toxicity, it should be acceptable for postoperative radiotherapy or chemoradiotherapy. For example, postoperative conformal radiotherapy, which enables a superior delineation of target volume and planning, is associated with improved survival and tolerable toxicities for patients with pT3N0M0 EC.²³

Conclusions

Previous RCTs mainly conducted in the late 20th century showed that PORT was not associated with improved survival (even a poor outcome in one RCT). However, these studies had many limitations, such as low sample size, two-dimensional radiotherapy technology, defects in the irradiation field, and inappropriate fractional and total irradiation dosages. Many studies included patients with paraaortic lymph node metastasis or cardiac adenocarcinoma. An increasing number of studies, mainly non-RCTs, have indicated that PORT with or without chemotherapy can improve survival for patients with

a poor prognosis (i.e., positive nodal disease, stage III/IV disease) after upfront surgery. Additionally, almost all the non-RCTs and the published RCT compared CRT+S and S+CRT directly showed that there was no survival difference between these two groups. Both CRT+S and S+CRT have their own advantages and disadvantages, and therefore can be chosen for locally advanced EC in the clinical practice. There is a great dispute on the indication, target volume, TRD, time interval and complications of PORT with or without chemotherapy. Future studies will be needed to address the optimal subgroup populations for different treatment methods and to re-evaluate the role of PORT for EC in the new era of conformal radiotherapy.

Ethics approval

This study was approved by the institutional review board of the First Affiliated Hospital of Anhui Medical University.

Consent for Publication

All the authors have consented to the publication of this manuscript.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

No funding was provided in the generation of this work.

Disclosure

The authors declare that they have no competing interests.

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