Radiotherapy for Carcinoma of the Esophagus: Progress of Treatment and Research in China

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ABSTRACT Carcinoma of the esophagus is a common malignancy in China. Radiotherapy is one of the most important modalities of treatment. This article provides a review of the natural history of this disease, the results of radiotherapy for esophageal cancer and the recent advances in radiation techniques in China. Significant progress has been made in this area of research and treatment. Combined treatment modalities and new therapies are being evaluated and may be expected to contribute to improved patient outcomes and better palliation of symptoms in the future.

KEYWORDS: esophageal carcinoma, external beam radiation, intraluminal radiation, chemotherapy, combined modality therapy.

Esophageal cancer is one of the most common carcinomas in China. About 250,000 new cases are diagnosed in China every year, approximately one half of the annual morbidity rate in the world. According to the China Cancer Database,[1] from 1990 to 1992, the mortality rate from esophageal cancer was 17.38 per 100,000, 22.14 per 100,000 for the males and 12.34 per 100,000 for females. In China, esophageal cancer is responsible for 16.05% of all cancer deaths, resulting in a rank of fourth among common cancers. It also represents one of the most deadly tumors worldwide. The incidence of esophageal cancer varies in relation to nation, race, diet, and gender. Even within a single country, the incidence and mortality vary considerably with geographic location. Within China, a high frequency of this disease has been noted in the south area of Taihang Mountain in north China, where the incidence was 100 per 100,000 individuals and the mortality was 76.72～127.93 per 100,000, a rate nearly 500 times that of a low incidence area (0.22 per 100,000).

Treatment for Early-esophageal Cancer

Natural history

In 1982, Pei et al. [2] described the natural history of 23 early esophageal cancer patients. This study, which was conducted through 1981 in an endemic area, Ci Xian, Hebei province (north China), detected 72 early esophageal cancer patients through screening in the whole population over 30 years of age. Among the 72 cases, 23 patients refused any treatment, so the natural history of this disease could be described based on collected data. The result showed that there was a long period, ranging from 12 months to 55 months (averaged of 33.9 months), between diagnosis (screening test) and the development of dysphagia. But the advanced period (from dysphagia, obvious filling defect, niche sign, or stenosis on barium meal, to

death) came quicker, i.e. 3 to 24 months, with an average of 9.7 months. The time from diagnosis to death was 20 to 78 months, with an average of 43.6 months. Another study [3] published in 1976 described the results for development of 19 early-stage cases. Their data indicated the average time from early detection to swallowing symptoms was 32.5 months, with the advanced period being 10.5 months. The whole course had an average of 43 months.

Results of treatment

Surgery has been the most effective means to treat esophageal cancer resulting in significantly varied survival rates for different stages. From 1982 to 1994, several authors [4-6] reported a 5-year survival of 43.2% to 92.6% in patients with an early disease who had been treated by surgery. Radiotherapy is another effective and important treatment, especially for those who are elderly, or have poor cardiorespiratory function, or refuse surgery. The reported 5-year survival rates for patients who received radiotherapy for early disease ranged from 23.3% to 73.1% (Table 1).[7-10]

When the disease is so early that no symptoms or X-ray changes can be seen, the 5-year survival rate after surgery or radiotherapy is above 59.3%. When dysphagia or images develop, but still in an early stage, the 5-year survival rate decreases below 43.2%.

From previous studies, we conclude that asymptomatic patients diagnosed by a screening test have better survival than those with the symptoms, whether treated by surgery or radiotherapy. For those who refuse surgery or those who appear to be inoperable due to other medical reasons, radiotherapy is also effective and should be given without delay.

Radiation Therapy for Moderately Advanced and Advanced Esophageal Cancer

Although surgery is the choice of treatment for this advanced disease, less than one quarter of these patients are suitable for complete resection due to age, co-morbid status and extent of their disease at diagnosis. So these patients often undergo radiation therapy. Among 9,104 esophageal cancer patients treated from 1958 to 1986 in Beijing CAMS Cancer Hospital,[11] only 947 patients (10.4%) received only surgery, 692 patients (7.60%) were treated by radiotherapy followed by surgery, 159 patients (1.74%) underwent post-operative radiotherapy, while 6,501 patients (71.4%) received only radiotherapy, and 805 patients (8.84%) had chemotherapy or other means of treatment. Therefore, radiotherapy is also a very important modality. Chen et al. [12] from Beijing CAMS Cancer Hospital reported the results of using radiotherapy alone in 180 patients with resestable tumors. The 5-year survival rate was 23.3%, which was similar to that of surgery [6, 13-15] in China (Table 2). Then what can we conclude about the effectiveness of radiotherapy for advanced esophageal cancer? Yin et al.[16] reported in 1980 that 5-year survival of 3,798 patients treated with radiotherapy alone was only 8.3%. Twelve years later in 1992 Yang et al.[17] found a 5-year survival of only 13.3% in 1,160 patients. Both authors analyzed the pattern of failure and presumed that persistent local problems—uncontrolled primary and recurrent diseases were the main forms of failure. In Yin's study, local recurrence and lack of control caused 84.9% (1,132/1,334) treatment failure and in Yang's study it was 68.6% (796/1,160). Why was the local tumor control after radiation so poor? Isn't esophageal carcinoma sensitive to radiotherapy? Does conventional radiotherapy give too low a dose on the tumor target volume causing poor local control? To answer these questions, multiple factors should be investigated.

Improvement in technology of radiotherapy

With the development of imaging technologies such as computed tomography (CT), magnetic resonance imaging (MRI), endoscopic untrasonography (EUS), positron emission tomography (PET), radiation oncologists are now able to make more precise staging, prognosis judgements, and irradiation field design. New radiation technologies based on CT, 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), offer potential tools for precise dose prescription on the target volume.

As noted above, the 5-year survival rate after radiotherapy alone has been around 10% over the past 20 years (Table 3),[16-21] and local recurrence has been the main pattern of failure. Several prospective studies have been conducted to improve the radiation dose to the tumor or radiosensitivity. Therefore, we should ask one question first: is conventional radiotherapy able to deliver the prescribed dose to the tumor target volume? Over the past ten years, several authors have proposed that cold-spot areas exist within the tumor volume in patients treated with conventional radiotherapy.[22-24] Xiao et al.[25] conducted a study focusing on the dose distribution in conventional radiation assessed by a three-dimensional treatment-planning system. Three different CT-derived treatment plans were pre-

pared for each of 20 previously untreated esophageal cancer patients. A conventional treatment plan for a standard field (CVs), a conventional treatment plan for an enlarged field (CVe), and a conformal (CF) plan were considered for each patient. A gross target volume (GTV), a clinical target volume (CTV), and a planning target volume (PTV) were contoured by an oncologist based on barium ingestion, endoscopy, and CT images. The comparisons of the three plans are shown on Tables 4 and 5. So, the authors presumed that a conventional radiation technique could not offer the prescribed dose to the tumor target volume when a large-sized tumor was seen on CT imaging. Although applying an enlarged field increased the dose to the tumor, the adjacent radiosensitive structures, i.e. the lungs and spinal cord, would receive doses of radiation beyond tolerance. A 3-dimensional treatment planning system should be employed to keep the prescribed dose to the target volume and avoid delivering extra doses to the normal tissue. But, is 3-dimensional radiotherapy able to lower local recurrence by increasing the dose to the tumor? More data and studies would be needed to confirm the efficacy of this new technique.

Studies on time-dose effect

Accelerated proliferation of tumor cells during the course of fractionated irradiation treatment is believed to be one of the causes of local failures in the treatment of squamous cell carcinoma of the upper respiratory and digestive tracts. But in what time course does this occur? Some authors presume that accelerated proliferation occurs from the very beginning of radiation, while others believe it begins after four weeks following radiation. Theoretically, applying accelerated hyperfractionation radiotherapy may improve tumor local control by overcoming accelerated proliferation of tumor cells. Some authors in China have conducted randomized trials to investigate accelerated hyperfractionation radiotherapy in patients with esophageal carcinoma.

Whole course hyperfractionated accelerated (WCAHF) radiation therapy

In 2001, Peng et al. [26] randomized 216 patients with esophageal cancer for treatment by conventional fractionated (CF) radiotherapy and whole course hyperfractionated accelerated (WCAHF) radiotherapy. The criteria for patient inclusion were: biopsy-confirmed squamous cell carcinoma; ≤ 70 years old; Karnofsky Performance Status ≥ 70; lesion length ≤ 8 cm; being able to swallow solid food; no superclavicular lymph node involvement or distant metastasis; and being able to tolerate radiotherapy. The 110 patients in the CF arm received radiotherapy at 2 Gy daily, 5 days a week for 6 to 7 weeks, for a total dose of 60 to 70 Gy. The 106 patients in the WCAHF arm received radiation at 1.5 Gy twice daily with an interval of 6 hours, 5 days a week for 3.3 to 4 weeks, for a total dose of 51~60 Gy/34~40 fractions. The 1-, 3-, and 5-year survival rates for the CF group were 45.5%, 20.0% and 13.6%, and for the WCAHF group were 69.8% , 40.6% , and 33.0%, respectively. The differences were statistically significant ($P<0.01$). Meng et al.[27] in 1990 compared random CF radiotherapy with WCAHF radiotherapy in 72 patients with carcinoma of the thoracic esophagus. The 1-year survival rates for the two arms were 50% (18/36) and 77.8% (28/36), respectively, with a significant difference ($P<0.05$).

Late course accelerated hyperfractionated (LCAF) radiotherapy

The Department of Radiation Oncology of the Shanghai Cancer Hospital has been on the forefront for investigations of LCAF radiotherapy in China. They had begun prospective randomized studies on this project in 1988. In 1997, Shi et al.,[28] from the Shanghai Cancer Hospital, reported the long-term effects of LCAF radiotherapy in 85 esophageal cancer patients. All the patients conformed to the following: biopsy-confirmed as having squamous cell carcinomas, no older than 70, a performance status over 80, being able to swallow semi-solid food, no lesion longer than 8.0 cm, no perforation or active bleeding and without superclavicula lymph node involvement or distant metastasis. In the conventional fractionated (CF) arm, radiotherapy was delivered in 1.8 Gy daily, 5 days a week for 7.4 weeks, for a total dose of 68.4 Gy/38 fractions. The patients in the LCAF arm received the same fractionated irradiation as the CF arm for a dose of 41.4 Gy/23 fracions over 4~5weeks, followed by accelerated hyperfracionated irradiation using reduced fields, 1.5 Gy/fraction twice a day, for a dose of 27 Gy in 18 fractions. Thus, the total dose was 68.4 Gy/41 fractions/6.2 weeks. Survival rates at 5-years for the CF and LCAF arms were 15% and 34%, respectively ($P<0.05$). Local control rates for the two arms were 21% and 55%, respectively ($P<0.01$). The median time to a local recurrence was 8 months for the CF arm and 29.3 months for the LACF arm.

After the first positive results which favored LCAF radiotherapy were released, several similar conclusions [29-33] have been achieved in different hospitals in China

Table 1. The survival rates for patients with early esophageal cancer

Author	Year	Treatment	Number of cases	The 5-year survival (%)
Shao et al.[4]	1993	Surgery	204 (Tis 92)	92.6
Li et al.[7]	1995	Radiotherapy	52 (screening test)	73.1
Chen et al.[8]	1982	Radiotherapy	27 (screening test)	59.3
Shao et al.[5]	1994	Surgery	9107 (lesion≤ 5 cm)	43.2
Zhang et al.[6]	1982	Surgery	4310 (lesion≤ 3 cm)	43.9
Chen et al.[9]	1997	Radiotherapy	193 (lesion≤ 3 cm)	30.1
Ding et al.[10]	1996	Radiotherapy	40	52.5

Table 2. The survival rates of patients with resectable esophageal cancer

Investigator	Year of treatment	Treatment	Number of cases	The 5-year survival
Cancer Institute of Jiangshu Province [13]	1969~1973	Surgery	201	29.4% (59/201)
Zhang et al.[6]	1952~1978	Surgery	1290	23.5% (303/1290)
Shao et al.[14]	1965~1985	Surgery	2032	47.1% (958/2032)
Beijing CAMS Cancer Hospital [15]	1958~1992	Surgery	3099	30.4% (942/3099)
		Surgery	180	23.3% (42/180)
Chen et al.[12]	-	Radiotherapy	(82 patients refused surgery)	31.7% (26/82)

Table 3. The survival rates for patients treated with radiotherapy

			Survival rate (%)		
Investigator	Year of report	Number of cases	1-year	3-year	5-year
Shanghai Cancer Hospital [18]	1978	1023	48.4	19.4	14.6
Yin et al. [16]	1980	3798	38.1	13.1	8.3
Zhu et al. [19]	1988	2722	44.0	16.0	8.8
Yang et al. [17]	1992	1160	45.9	19.6	13.3
Chen et al. [20]	1994	1110	55.9	20.8	13.8
Ji et al. [21]	1998	780	50.6	17.1	10.5

Table 4. Comparison of dose distribution of CVs, CVe, and CF

	Prescribed dose (Gy)	GTV coverage (%)	CTV coverage (%)	Mean dose in GTV (Gy)	Minimum dose in CTV (Gy)
CVs	60	36.6	27	44	15.8
CVe	60	38.0	33	57	48.6
CF	60	100	95	62	57

Abbreviation: CVs, standard field; CVe, enlarged field; CF, conformal.

Table 5. Comparison of dose on lung and spinal cord

	Lung V20	Mean lung dose (Gy)	Spinal cord maximum (Gy)
CVs	23%	11.6	38.9
CVe	31%	15.4	45.3
CF	20%	11.3	9.1
P	0.002	0.008	0.026

Table 6. The survival rates for patients treated with late-course accelerated hyperfractionated (LCAF) radiotherapy and conventional fractionated (CF) radiotherapy

	1-year survival rate (%)		3-year survival rate (%)	
Investigator	LCAF	CF	LCAF	CF
Shi et al. [28]	72.1	47.6	41.9	19.0
Han et al. [29]	84.0	62.0	48.0	22.0
Guo et al. [30]	81.0	47.6	57.1	19.0
Zhou et al. [31]	56.1	57.5	29.3	22.5
Niu et al. [32]	64.3	39.3	39.3	10.7
Yang et al. [33]	77.4	53.3	45.2	20.0

(Table 6). In 2001, a meta-analysis pooling six randomized trials which compared CF radiotherapy with LACF radiotherapy was carried out by Zou et al.,[34] showing that the 1- and 3-year survivals for a LCAF group were 2.43 times of that of a CF group and that LCAF radiotherapy was superior to CF radiotherapy. In 2003, Yang et al. [35] reported that the 4-year survival of a LCAF group was 31.3% and that the local control rate was 45% compared to 19.6% and 22.8% for a CF group, but the differences were not statistically significant (P=0.22; P=0.08). From 2003 to 2004, 13 studies have been completed comparing CF radiotherapy with LCAF radiotherapy. Most of these studies had a positive result favoring the latter, though with limited cases. A large scaled, multi-center randomized study with standard eligibility is needed to further evaluate the role of LCAF radiotherapy.

Rate of cancer absence in the esophagus after radiotherapy

In 2001, Xiao et al. [36] from the Beijing CAMS Cancer Hospital published the autopsy results of patients who had died after radiotherapy. Nine of the 32 patients (28.1%) who had received a radical dose of a radiation showed no residual tumor in the esophagus, 71.9% patients had a residual tumor, 46.9% patients had lymph node metastasis, and 37.1% patients had visceral metastasis. Among the 32 patients, 24 (75%) had died from perforation of the esophagus, with one third of the perforations due to infection and not residual cancer. Wang et al.[37] also reported that no cancer was observed in a resected specimen from the esophagus in six of 28 (21.1%) patients who had a local clinical recurrence after radiotherapy. Since there are a certain portion of patients who are cancer-free after radiation, it should be noted that a local recurrence must be confirmed by biopsy in order to avoid unnecessary anticancer measures.

Combination of surgery and radiotherapy

Preoperative (neoadjuvant) radiotherapy

From 1960 to 1986, Zhang et al.,[38] from the Beijing CAMS Cancer Hospital identified 276 esophageal cancer patients, whose tumor was locally advanced and marginally resectable based on consultations between surgical and radiation oncologists. These patients received preoperative radiotherapy at a dose of 40 Gy. Surgery was performed 2 to 4 weeks after the completion of the radiotherapy. The 5-year survival of the 276 patients was 29.7% compared to only 19.2% in 736 patients who had surgery alone during the same period (P<0.001). Ji et al.[39] reported the results of preoperative radiotherapy in 116 patients with locally advanced esophageal cancer admitted from 1990 to 1994. Compared with 466 patients who only had an operation, patients who received combined therapy had a slightly higher 5-year survival (34.3% *vs.* 30.1%), with no significant difference. Morbidity within 30 days after operation and resectability were similar between the two groups (2.6% *vs.* 2.6%, 93% *vs.* 94%, respectively). Wang et al.[40] from the Beijing CAMS Cancer Hospital randomized 418 patients with an operable carcinoma to preoperative radiotherapy (n=195) or surgery alone (n=223) and achieved a significantly better survival for preoperative therapy (P=0.042). Similar surgical mortality (2.2% *vs.* 4.2%) was observed in the two groups. Lower incidence in lymph node metastases (22.2% *vs.* 40.8%, P<0.001) and local-regional recurrence (22.7% *vs.* 41.4%, P=0.01) were observed in the preoperative arm compared to the surgery alone arm. Ou et al.[41] analyzed the correlation between the pathological response to radiotherapy and the survival rate. They found the 5-year survival in patients with a severe response (pCR), intermediate response, and mild response to radiotherapy was 60.7%, 46.4%, and 21.1%, respectively, with a significant difference between the groups. Patients who had a severe response to radiotherapy had a significantly better 5-year survival compared with the surgery-alone group (38.8%) (P=0.000). Survival of the intermediate response group and the surgery-alone group was similar (P=0.295). Patients with a mild response had inferior survival compared with the surgery-alone group (P=0.034). This study concluded that preoperative radiotherapy offered no benefit for those who were not sensitive to radiation.

Postoperative radiotherapy

The rationale of postoperative radiotherapy for patients with esophageal cancer is based on the high incidence of local reccurence after surgery. The outcome for resectable patients is still gloomy—the majority of postoperative patients die of local recurrence or distant metastasis within two years. In 1984, Huang et al. [42] reported that, due to recurrence or metastasis, 77.4% of esophageal cancer patients who underwent surgery died within two years after operation, and 40% of the survivors died within 5 years and 24.2% within 10 years.

Several articles concerned with the effectiveness of prophylactic radiotherapy after radical resection of esophageal cancer have been published[43-46] worldwide.

Most of these studies delt with a patient group less than 200, and found that postoperative radiotherapy reduced a recurrence in the irradiation field but did not improve the survival. Fok et al.[43] from Hong Kong, applied postoperative radiotherapy which was delivered in 3.5 Gy per fraction, three times a week, for a total dose of 49 to 52 Gy/14 fractions, and found a significantly higher incidence of gastric hemorrhage or gastrelcosis (37%) compared with the control group (6%). Teniere et al.[44] in France randomized 221 patients to postoperative radiotherapy (55.8 Gy/6 for 7 weeks) or surgery alone and showed no survival advantage for adjuvant therapy. Zieren et al.[45] in Germany randomized 68 patients to postoperative radiotherapy (45 to 55 Gy/5 for 6 weeks) or surgery alone with no difference in the 5-year survival between the groups. The negative results of above two studies could have been due to insufficient number of patients. Xiao et al.[47] from the Beijing CAMS Cancer Hospital randomized 549 patients, who had undergone radical resection, to a surgery-alone group (S) of 275 pateints or a surgery plus radiotherapy group (S+R) of 220 patients (54 patients were excluded because of incomplete radiotherapy). Radiation treatment was started 3 to 4 weeks after the operation. The portals encompassed the entire mediastinum and bilateral supraclavicular areas. A 50-Gy dose was delivered to the supraclavicular area and 50 to 60 Gy in 25 to 30 fractions over a period of 5 to 6 weeks to the mediastinum. The overall 5-year survival rate is shown on Table 7. The incidence of recurrence in the supraclavicular and neck regions, the chest, and at the anastomosis, was apparently lower in the S+R group compared to the S group, 3.1% *vs.* 13.2%, 16.8% *vs.* 25%, 0.5% *vs.* 5.8%, respectively ($P<0.05$), but similar in the abdomen or via the blood ($P>0.05$). Early side effects related to the radiation treatment were observed in about one third of the patients such as nausea, anorexia and leucopenia (7.3%). Late complications included radiation lung injury (fibrosis) (2.3%) and noncancerous pericardial effusion or pleural effusion in 3.2% of the patients. The frequency of anastomotic stenosis was 1.8% in the S group and 4.0% in the S+R group, with no significant difference. The conclusions of this study were that postoperative prophylactic radiotherapy reduced the in-field recurrence in all patients and improved the 5-year survival rate for patients with stage III disease, without increasing the frequency of anastomotic stenosis. Although the 5-year survival rate was increased for patients with positive lymph nodes (N1), the role of postoperative radiation in such patients still needs to be confirmed (Table 7). The data from this study was reviewed retrospectively by the prsent author [48] and an influence of the number of metastatic lymph nodes on survival was found through multivariate analysis. According to the extent of metastasis, all the patients were classified into three groups: Group 1, 269 patients (49.0%) without lymph node involvement; Group 2, 159 patients (29.0) with one to two positive nodes; and Group 3, 121 patients (22.0%) with three or more positive lymph nodes. For the same T3 and Stage III, the 5-year survival rate for Groups 1, 2, and 3 was 50.6%, 29.3%, and 11.7%, respectively ($P= 0.0000$). For patients with Stage III, the 5-year survival rates for Groups 1, 2, and 3 are shown in Table 8. The author suggested that an additional classification including the number of lymph nodes is feasible —in the Stage III lesions, an absence of positive lymph nodes should be denoted IIIA, one to two positive lymph nodes should be denoted IIIB, and three or more positive lymph nodes should be denoted IIIC (Table 8).

Chemoradiotherapy

The role of chemoradiotherapy in patients with esophageal cancer has been intensely investigated in China since the 1990s. Wang et al.[49] randomized 80 patients to a group receiving chemotherapy (cisplatin, mitrocaphane, and pingyangmycin) plus 60 to 70 Gy of radiotherapy or a group treated with radiotherapy alone, and found a significantly better survival in the chemoradiotherapy group at 1, 2, and 3 years (75%, 47.5%, and 37.5%, respectively) compared with radiotherapy alone (52.5%, 35%, and 25%, respectively). Wang et al.[50] randomized 180 patients to a group treated with concurrent chemoradiotherapy or radiotherapy alone. There was a significant better 5-year survival rate in the chemoradiotherapy arm compared with the radiotherapy-alone arm, 16.2% to 30% (using different regimens) vs. 9.4%. Zhang et al.[51] randomized 192 patients to a radiotherapy (60 to 70 Gy) group followed by chemotherapy (cisplatin and 5-Fu) or a radiotherapy-alone group. A significant survival advangtage favored the chemoradiotherapy arm with 1, 2, and 3-year survival rates in the chemoradiation therapy group of 61.5%, 44.8%, and 34.4% versus 45.8%, 31.3%, and 18.8% in the radiotherapy-alone group (Table 9).

Although almost all reported studies have favored chemoradiotherapy to radiotherapy alone, the role of chemoradiotherapy still needs to be further investigated before it is recommended as a standard therapeutic

Table 7. The survival rates of patients treated with postoperative radiotherapy

Investigaor	Treatment	Number of cases	Survival rate (%)			P
			1-year	3-year	5-year	
Teniere et al. [44]	S+R	102	-	-	18.6	1.62
	S alone	119	-	-	17.6	
Zieren et al. [45]	S+R	33	57.0	22.0	-	NS
	S alone	35	53.5	20.0	-	
(Stage III)	S+R	11	41.0	18.0	-	NS
	S alone	13	47.0	19.0	-	
Xiao et al. [47]	S+R	220	79.3	50.9	41.3	0.4474
	S alone	275	79.1	43.5	37.1	
(Stage III)	S+R	129	75.5	43.2	35.1	0.0027
	S alone	143	67.5	23.3	13.1	
LN (+)	S+R	129	72.3	38.2	29.2	0.0698
	S alone	132	69.7	24.7	14.7	

Abbreviation: S-surgery; R-radiotherapy; NS-not signifcant.

Table 8. The 5–year survival rates of patients after surgery

	Group 1	Group 2	Group 3	P
T3	50.6%	29.3%	11.7%	0.0000
Stage III	58.1%	30.6%	14.4%	0.0092

Group 1: N0; Group 2: N1, 1-2 positive lymph nodes; Group 3: N1, ≥ 3 positive lymph nodes.

Table 9. The survival rates of patients receiving chemoradiotherapy compared with radiotherapy alone

Author	Year	Number of cases	Treatment	1-year (%)	3-year (%)	5-year (%)
Wang et al.[49]	1992	80	CT+RT	75.0	37.5	-
			RT	52.5	35.0	-
Wang et al.[50]	1995	180	CT+RT	-	-	16.2~30.0
			RT	-	-	9.4
Zhang et al.[51]	2000	192	CT+RT	61.5	34.4	-
			RT	45.8	18.8	-

CT: chemotherapy; RT: radiotherapy.

regimen. Large-scale, multi-center, randomized trials are being anticipated.

Intralumianl radiotherapy and combined external and intraluminal radiotherapy

Intralumianal brachytherapy (ILBT) combined with external beam radiation therapy (EBRT) has been proposed as an additional method to increase local control and overall survival in patients with advanced esophageal cancer. Very little data from treating this disease with ILBT alone are available. In 1982 Miao et al.[52] from the Beijing CAMS Cancer Hospital reported the results of 203 patients with esophageal cancer who were treated with an intracavity appliance (Co-60). The 1-, 3-, and 5-year actual survival was 34.5% (70/203), 13.8% (28/203), and 8.4% (17/203), respectively. It should be noted that 21.4% of the patients had lesions less than 3 cm in length and 44.4% patients had lesions 3 to 5 cm long. The 5-year survival rates for superficial and infiltrated disease were 26% (7/27)

and 5.7% (10/176), respectively. Intracavity radiotherapy was relatively effective for patients with early stage or superficial disease, with a high incidence of acute esophagitis (66%) and stenosis (11.8%). More data from combined ILBT and EBRT as a method of treatment has been published.

Chang et al.[53] randomized 72 patients to a ILBT and EBRT group or a group treated with EBRT alone, and found no significant difference between the two groups. The 1-, 3-, and 5-year survival, and local control rates in the combination group and control group were 66.7%, 35.1%, 17.9%, and 64%, versus 72.7%, 26.5%, 14.7%, and 61%, with no significant difference.

Zhu et al.[54] reported the results in treating 129 patients with esophageal cancer who received different treatment schedules. The patients were randomized to four groups: Group A, EBRT alone (n=33); Group B, 50 Gy EBRT in 25 fractions over 5 weeks followed by 15 to 16 Gy ILBT in 3 fractions over 3 weeks (n =32); Group C, same EBRT and ILBT as Group B with additional daily carboplatin of 100 mg over 5 days (n= 31); Group D, same EBRT as Group A and same chemotherapy as Group C (n=33). The median survival time for Group A, B, C, and D was 12, 18, 13, and 16 months, with no significant difference between the groups. Patients in Group D had a significantly better overall survival and cancer-free survival at the third-year compared with those in Group A, 39.4% and 36.4% versus 15.2% and 15.2% , respectively (P=0.048). Patients in Group B had a 43.8% incidence of esophageal stenosis, higher than any other group, whereas the incidence in Group A, C, and D was 15.2%, 38.7%, and 12.1%, respectively. In Group A, 55.2% patients died of a local recurrence, whereas death occurred in 22.2% of Group B and 21.4% of Group C, respectively (P=0.012). Therefore, the author presumed that ILBT combined with EBRT could reduce the local recurrence but could not improve survival. The high incidence of esophageal stenosis observed in the ILBT plus EBRT group might have a negative impact on the long-term survival.

In 1999 Wang et al.[55] randomized 252 patients with moderately advanced esophageal cancer to receive EBRT of 50 to 60 Gy (Co-60) in 25 to 30 fractions followed by ILBT of 10 Gy to 21 Gy (Ir-192) in 2 to 3 fractions plus chemotherapy using carboplatin (Group A, n=84), the same EBRT and ILBT without chemotherapy (Group B, n=84), or EBRT alone at a dose of 64 to 70 Gy in 32 to 35 fractions (Group C, n=84). The 3-year survival rate for each group was 42.8%, 32.1%, and 17.9%, respectively, with the results showing a significant difference (P<0.01). Patients in Group A and Group B had a better remission of dysphagia, together with a higher incidence of odynophagia, compared with that in Group C.

ILBT allows improvement of dysphagia for patients with advanced esophageal cancer, with a remission rate ranging from 39% to 91% and remission time as long as 67.7 weeks (according to the data from domestic conferences). For patients having recurrent or uncontrolled disease after definite EBRT, ILBT provides another therapy without adding the dose to the spinal cord. In 1995 one author reported a 6.4 ± 2 month average-survival time and a 30% remission rate of dysphagia in 30 patients with recurrent disease who received ILBT at a dose of 10 Gy to 21 Gy in 2 to 3 fractions.

In summary, ILBT is effective for superficial esophageal cancer due to the character of dose distribution. For late-stage disease, ILBT definitely provides palliation of dysphagia. As a boost to EBRT, ILBT allows improved local control with a high incidence of severe complications which affects quality of life. Few large-scale studies have been reported recently in China.

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