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Original Article

Evaluation of Complications and Treatment Outcomes Following Intraluminal Brachytherapy after Definitive Chemoradiation in Patients with Esophageal Cancer

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Abstract

Background: Limited data exist on complications and treatment outcomes following brachytherapy after chemoradiation in esophageal cancer. This study aimed to assess complications and treatment outcomes after intraluminal brachytherapy post-definitive chemoradiation.

Methods and Materials: This retrospective cohort study included esophageal cancer patients treated at Imam Reza Radiotherapy Center, Mashhad, Iran (2016-2023). Patients received chemoradiotherapy with paclitaxel-carboplatin, cisplatin-irinotecan, or cisplatin-5-FU (5-6 weeks), with a total radiation dose of ≥45 Gray. After a two-week rest, they underwent HDR brachytherapy with cobalt-60 and were followed monthly for one year.

Results: A total of 125 patients (mean age: 71.08±10.67 years) were evaluated. The overall survival (OS) and disease-free interval (DFI) were 47.26 and 22.62 months, respectively. The most common tumor location was the middle esophagus, and the most common grade was G2. An ECOG score <2 was observed in 96 patients. No significant association was found between OS and DFI with tumor location, grade, dysphagia level, or functional index. However, brachytherapy dose, radiotherapy dose, and chemotherapy regimen were significantly associated with OS, but not with DFI. Post-treatment complications occurred in 98 patients, including local recurrence in 39 cases. Patients without complications had a mean DFI and OS of 54 and 55 months, respectively, while those with complications had 37 and 50 months. Complications were significantly associated with DFI but not with OS. Complete response was seen in 106 patients, significantly correlating with OS (P=0.003) and DFI (P<0.001). Patients with local and distant recurrence had an 11-fold higher mortality risk.

Conclusion: Intraluminal brachytherapy after definitive chemoradiation plays a crucial role in treatment management for esophageal cancer. It should be considered as a treatment option, but further studies with larger sample sizes are needed for routine implementation.

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Keywords:
Brachytherapy
Esophageal Cancer
Definitive Chemoradiation
Overall survival

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1. INTRODUCTION

Esophageal cancer is a malignant tumor originating from the cells lining the esophagus (1). Its prevalence is high in Asian countries, especially in the northern areas of Iran, forming a region known as the "Esophageal Cancer Belt" extending from northern Iran to Central Asia and China. According to the Iranian National Cancer Registry, esophageal cancer is the second most common cancer in men and the fourth in women. Dysphagia is the most common symptom in Iranian patients, which occurs in the advanced stages of the disease and also causes severe weight loss (2). Globally, esophageal cancer is the eighth most common cancer, with an estimated 604,100 new cases and 544,076 deaths in 2020. Its incidence rate has been higher in men, and its onset typically occurs between 50 and 70 years of age (3).

Esophageal cancer is considered as one of the deadliest types of cancers due to its rapid progression and poor prognosis. The 5-year survival of these patients is reported to be about 20% (4). This low survival rate can be attributed due to the late diagnosis of the disease, which is in turn due to the late appearance of its major symptoms such as difficulty swallowing (dysphagia) in the advanced stages of the disease (5). Several risk factors for esophageal cancer have also been identified, including smoking and other forms of tobacco, alcohol consumption (6), obesity (7), human papillomavirus (HPV) infection (8, 9), hepatitis virus (HCV) infection (10) and family history (11).

Based on histological features, esophageal cancer is classified into squamous cell carcinoma (SCC) and adenocarcinoma. Diagnosis is made using imaging techniques such as endoscopic ultrasound (EUS), computed tomography (CT), and positron emission tomography (PET) scans. During endoscopy, the inner layer of the esophagus is closely examined. If cancer is suspected, a biopsy may be performed from the suspected area to provide a more accurate diagnosis for esophageal cancer. After the biopsy, the stage of the disease is classified according to the TNM system. The PET-CT method is one of the newest imaging methods that uses a combination of two methods, Positron Emission Tomography (PET) and Computed Tomography (CT). The most common use of PET-CT for esophageal cancer staging is related to the spread of cancer to distant areas. Also, it can be used to monitor the effectiveness of treatment and identify cancer recurrence; PET-CT can further help doctors in making treatment decisions, such as surgery or radiotherapy (12, 13). Additionally, magnetic resonance imaging (MRI) is used for esophageal cancer diagnosis, offering slightly higher accuracy (DW-MRI) compared to PET-CT. MRI can also help determine the cancer stage and detect recurrent disease (13).

Treatment options for esophageal cancer include surgery, chemotherapy, radiotherapy, or a combination of these methods. These options are mostly determined by the cancer site and stage. In very early stages of esophageal cancer, surgery is used as the primary treatment method. For advanced stages, a combination of chemotherapy, radiotherapy and then surgery is preferred (4). Radiation therapy is a common treatment that can be used alone or in combination with other therapies. In the surgical method alone, the overall survival rate is reported to be low, which is accompanied by local and distant spread. However, in the treatment of unresectable cancers, other treatments have been considered, such as combined chemotherapy and radiotherapy, reported in clinical trials to be more effective than radiotherapy alone (14). This combined chemoradiotherapy method is beneficial as a neoadjuvant therapy before surgery. In some cases, radiotherapy is performed after surgery to reduce the risk of local recurrence and potentially increase patient survival. Although various studies have shown that this reduces local recurrence in tumors with involved margins, it has not been associated with increased overall patient survival and requires further investigation for approval (14).

Among the most common symptoms of esophageal cancer, dysphagia significantly impacts patients' quality of life. Consequently, several local treatment options have been proposed to manage dysphagia, including intraluminal stenting, laser therapy, alcohol ablation, external beam radiation therapy (EBRT), and brachytherapy (5). Currently, there is no consensus on the superiority of any of these treatments over others. On the other hand, intraluminal brachytherapy can be more effective in increasing patient survival than other endoscopic methods. However, this method also requires appropriate dosimetry and consideration of patient's individual characteristics (5). By definition, intraluminal brachytherapy is one of the esophageal cancer treatment methods that uses gamma rays or proton rays to destroy cancer cells inside the esophagus. In this method, a radiation source is placed inside the esophagus, and its rays are directed to the surrounding tissues. Although it transfers a highly lethal dose of radiation to the cancer cells, it is among the low-risk treatments for esophageal cancer and a much lower dose reaches the healthy tissues surrounding the tumor.

Intraluminal brachytherapy is usually used for patients who cannot tolerate external radiotherapy due to old age, co-morbidities, or other reasons. In some cases, it may be used as one of the combined treatment methods. For

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intraluminal brachytherapy, a 6 to 10 mm applicator is used, which is inserted into the esophagus transnasally or transorally. The radiation source can remain inside the esophagus from a few minutes to an hour, and is then removed. In addition, brachytherapy is often used in combination with external radiotherapy in patients with poor performance status who may not tolerate aggressive chemotherapy methods. It has been reported to be effective in the local control of tumors as well as relieving symptoms of advanced or recurrent diseases (4). However, one of the problems of using intraluminal brachytherapy in esophageal cancer is the high probability of complications and tissue destruction at high doses. Larger applicators are used in a wide esophageal lumen, while the use of small diameter applicators is limited to the treatment of obstructive lesions. Dosimetry for determining the appropriate dose in brachytherapy is based on the diameter of the lumen, the diameter of the applicator, and the dose that is transferred from each 5 mm of the applicator surface to the esophagus wall; the dose of each applicator is ultimately determined by these criteria (15). But why brachytherapy is less commonly used is because of the need for high expertise, lack of definitive evidence, the risk of serious complications, and lack of acceptance of this method. Nevertheless, this method can be considered as a suitable option for useful and quick relief of disease symptoms along with good quality of life and more appropriate treatment doses. Therefore, further research is needed to develop methods for controlling its complications and facilitating its use (16).

Another treatment for esophageal cancer is definitive chemotherapy, which is performed along with external radiotherapy. But it is warned that intraluminal brachytherapy should not be used as a concurrent treatment with chemotherapy in patients with esophageal cancer. However, intraluminal brachytherapy has several advantages for these patients, including targeted treatment, increased effectiveness, and less invasiveness. Also, for some patients with esophageal cancer and limitations of age, overall health status and other factors, intraluminal brachytherapy can be a suitable alternative. It should be noted that although intraluminal brachytherapy has several advantages for patients with esophageal cancer, each patient's specific condition and medical history should be taken into account in choosing the best treatment plan for each individual.

The results of other studies showed that intraesophageal brachytherapy 2 to 3 weeks after the completion of definitive chemoradiotherapy for patients with esophageal cancer can have a significant improvement in treatment outcomes, along with fewer side effects than other treatment methods (17). In addition, side effects after intraluminal brachytherapy, including esophagitis, bleeding, nausea, and vomiting, were mostly manageable. Since the standard treatment of esophageal cancer currently includes neoadjuvant chemoradiotherapy and then esophagectomy, several treatment options have been proposed that can be chosen by the therapist's evaluations of the individual patient's condition.

Also, it seems that intraluminal brachytherapy method has been used for some time but has not been addressed for various reasons; now it can be considered as an option that has the potential for further adjustment and benefit for patients; it can also open a new path in the treatment, relief, and improvement of quality of life for esophageal cancer patients. To address this issue, the present study was designed and conducted with the aim of evaluating the complications and treatment outcomes in patients with esophageal cancer following intraluminal brachytherapy after definitive chemoradiation.

2. METHODS AND MATERIALS

This study was a retrospective cohort study. The study data was collected from all patients with esophageal cancer admitted to Imam Reza Radiotherapy Center in Mashhad, Iran between 2016 and 2023 who were candidates for definitive chemoradiotherapy treatment and met the inclusion criteria. Relevant information was collected through a pre-designed checklist and clinical examination by a radiation oncologist. Two categories of primary and secondary data were collected. Primary data included the patients' complete clinical response to treatment, and secondary data included findings from their quality of life, local recurrence, distant metastasis, overall survival, disease-free interval and other demographic variables (**Table 1**).

Exclusion factors included the following: pregnancy and breastfeeding, cervical esophageal cancer, simultaneous involvement of the stomach, fistula between esophagus and bronchus, ulcerative tumors, severe stenosis or obstruction of the esophageal lumen that requires dilatation before brachytherapy, multiple and scattered lesions, involvement length greater than 10 cm, relapsed disease, metastatic involvement, as well as patient refusal to participate in the study.

In this study, histological confirmation and minimal gastrointestinal endoscopy, CT scans of abdomen, pelvis and chest, as well as endoscopic ultrasound (EUS) were used to definitively diagnose esophageal cancer in patients. After biopsy, disease staging was determined according to the TNM system. All selected samples were evaluated for the need for brachytherapy and definitive chemoradiation. The

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Table 1. Variables examined in the study and their practical definitions

Variable	Definition
Age	The number of years in a patient's lifetime
Gender	Phenotype of the individual
Tumor location	The exact anatomical location of the tumor in the esophagus (proximal, middle, inferior)
Response to treatment	Tumor response rate (either complete or incomplete) by endoscopy and imaging within one month after the end of brachytherapy
Tumor malignancy grade	Tumor grade based on pathology report (Grade 1 to 3)
Tumor size	Tumor size based on pathology report (in centimeters)
Dysphagia levels	Levels of dysphagia by the patient's history (Grade 1 to 4)
Functional index (staging)	Functional status with 5 severity levels of staging based on AJCC
Chemotherapy regimen	Type of chemotherapy regimen
Brachytherapy dose	Frequency of brachytherapy sessions (in Gray)
Radiotherapy dose	Radiotherapy dose (in Gray)
Side effects	Complications after treatment: esophageal stricture, perforation, dysphagia, and odynophagia
Local recurrence of metastasis	Residual tumor in endoscopy or imaging and /or new lesion in during periodical follow-up with imaging
Disease-free interval (DFI)	The time interval (in months) from the end of brachytherapy to the absence of tumor observation, periodical follow-up with endoscopy or imaging
Overall survival (OS) of each patient	Time interval from the end of brachytherapy to the death of the patient (in months)
Vital status	Individual's vital status (either alive or deceased)

mentioned information was extracted from the patients' files and included in the checklist.

Patients were treated with chemoradiation according to the therapist's standard method with a regimen of either paclitaxel and carboplatin or cisplatin and irinotecan or cisplatin and fluorouracil for 5 to 6 weeks with a total radiotherapy dose of at least 45 Gray. After a 2-week rest, HDR brachytherapy with cobalt-60 was performed with a total dose of 10 Gray (2*5 Gray). The diameter of the esophageal brachytherapy applicator was 8 to 13 mm, which was inserted into the esophagus by a guide wire and fixed in place. Brachytherapy was irradiated with a dose of 10 Gray to a depth of one centimeter of the catheter center. The American Brachytherapy Society has published guidelines for achieving a specific therapeutic dose in brachytherapy, which were found useful in selecting the appropriate applicator. Accordingly, an applicator with an outer diameter of 6 to 10 mm and a dose of 5 Gray per fraction in one to four sessions is recommended and used, depending on individual patients' clinical condition (18).

The patients' treatment outcomes and complications evaluated in this study included tumor size, tumor grade, tumor location (distance between tumor and incisor teeth in endoscopy), presence or absence of distant metastasis, local recurrence, presence or absence of lymph node involvement, survival prediction, response to treatment and complications such as stenosis, perforation and odynophagia. Therefore, the patients were followed up monthly for one year after brachytherapy in terms of treatment complications and quality of life. For recurrence evaluation, patients underwent endoscopy or CT scans of the chest, abdomen, and pelvis based on their symptoms, in order to assess progressive dysphagia. Quality of life was assessed by the ECOG scale (7), designed by Zubrod et al. in 1960; it included 5 items in which the patients' functional status was scored from zero (i.e., fully active and normal) to five (i.e., deceased). Based on previous studies, the patients of the present study were divided into two groups according to their ECOG performance status: those with a favorable performance status (< 2) and those with an unfavorable performance status (≥ 2).

Since dysphagia is one of the significant symptoms in assessing the effectiveness of the treatment and monitoring disease status and its recurrence, the classification of dysphagia was defined as follows according to a similar study (7):

0 = no dysphagia;
1= difficulty to swallow some solid food;
2 = difficulty to swallow some semisolid food;
3 = difficulty to swallow liquid food;
4 = absolute dysphagia.

2.1. Data Analysis

Collected data were entered into SPSS software. Non-parametric survival analysis tests such as the life expectancy table, Kaplan-Meier product limit method, log-rank test, and Cox regression analysis were used to analyze the data. The

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relationship between the variables and disease-free interval and overall survival were analyzed and reported.

3. Results

In this study, a total of 125 patients with esophageal cancer were included and examined, of which 49.6% were male (n=62) and 50.4% were female (n=63). The patients' mean age was 71.08±10.67 years, and ranged from 32 to 95 years old. The smallest tumor size was 4 cm and the largest was 10 cm, with a mean size of 6.32 cm. The patients' mean overall survival (OS) and disease-free interval (DFI) were 47.26 and 22.62 months, respectively **(Table 2)**.

3.1. Distribution of dysphagia grades

Before starting the treatment, distribution of different grades of dysphagia were observed as follows: grade one (n=51), grade two (n=60), grade three (n=7), and grade four (n=7). Involvement of the thoracic areas of esophagus were seen in the middle (n=60; 48%), lower (n=52; 41.6%) and upper part (n=1). In addition, 12 patients (9.60%) showed involvement of both the upper and middle parts of the thoracic esophagus **(Figure 1)**

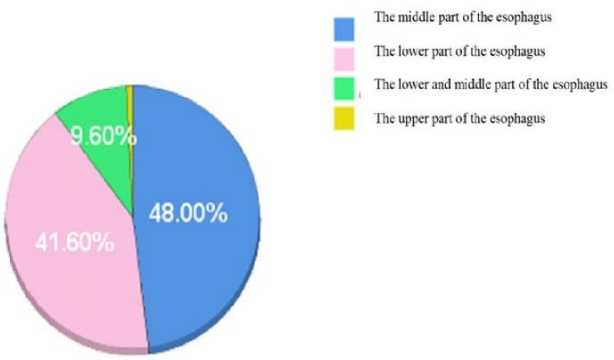

Figure 1. Distribution of anatomical tumor location in the esophagus

3.2. Distribution of tumor grades and metastases

In examining the tumor grade, 32, 81 and 12 patients had tumors with grades one (G1), two (G2) and three (G3), respectively. Also, in the evaluation of functional index (ECOG), 96 patients showed ECOG less than 2, while 29 patients had ECOG greater than or equal to 2. During the course of treatment, patients developed metastases to various organs, with the most common metastasis occurring to the lungs (16%). Additionally, bone, lung, liver, and brain metastases were recorded in 2, 20, 8, and 2 patients, respectively (Figure 2).

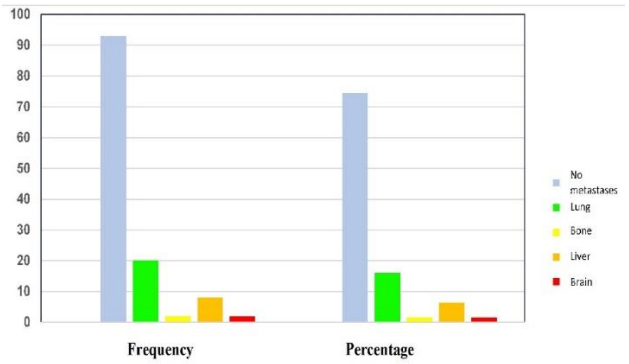

Figure 2. Frequency and percentage of metastases to different body organs

3.3. Distribution of local or distant recurrence

After the end of brachytherapy, during periodic follow-ups with endoscopy or imaging (barium swallow or CT scan), 68.8% of patients (n=86) showed no evidence of local recurrence, while the rest of the patients had findings suggestive of local recurrence on endoscopy or imaging in different parts of the esophagus or lymph nodes **(Table 3)**.

3.4. Distribution of complications

Following intraluminal brachytherapy after definitive chemoradiation, no complications were observed in 27 patients, but 80 patients showed different degrees of dysphagia. Out of these, 54 patients had no evidence of local recurrence on endoscopy or imaging, 11 patients had esophageal stricture in the endoscopy report that required bouginage, and 8 of these 11 patients showed evidence of local recurrence. Also, 7 patients faced painful swallowing problem (odynophagia), of which 4 patients showed evidence of local recurrence. Only one patient without evidence of side effects was found to have recurrence in the lower esophagus and metastases to the lung.

3.5. Chemotherapy regimens and radiation doses

The most commonly used chemotherapy regimen included 5 sessions of PACI+CARBO (n=98), followed by chemotherapy regimens; 5 sessions of CIS+IRINO (n=8) and 2 sessions of CIS+5FU (n=19). The total radiation dose for 93 patients was more than 50 Gray, while the remaining 32 patients were irradiated with a dose of 45 to 49.9 Gray. Also, patients underwent brachytherapy 1 to 4 times with a dose of 5 Gray, most of them included patients with 2 or 3

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Table 2. Patients' characteristics and quantitative information

Variables	Minimum	Maximum	Mean	Standard Deviation
Age (years)	32	95	71.08	10.67
Tumor size (cm)	4	10	6.32	1.74
DFI (months)	1	91	22.62	20.85
OS (months)	1.5	91	**47.26**	20

Table 3. Frequency and percentage of local recurrence in the course of treatment

Local Recurrence	Frequency	Percentage
Middle thoracic	17	43.6
Lower thoracic	3	7.6
Upper thoracic	17	43.6
Lymph nodes	2	5.2
Total	39	100

Table 4. Frequency distribution of other variables in the study patients

Variables		Frequency	Percentage
Chemotherapy regimen	PACI+CARBO (5 sessions)	98	78.4
	CIS+IRINO (5 sessions)	8	6.4
	CIS+5FU (2 sessions)	19	15.2
Total radiation dose	45-49.9 Gray	32	25.6
	More than 50 Gray	93	74.4
Total brachytherapy dose	5 Gray	1	0.8
	10 Gray	58	46.4
	15 Gray	58	46.4
	20 Gray	8	6.4

treatment sessions (10 or 15 Gray) and only one patient received 1 brachytherapy session (**Table 4**).

3.6. The patients' overall survival

3.6.1. The patients' overall survival and tumor grade and location

The mean overall survival (OS) of patients with mid-thoracic tumors was 43.74 months, while it was 53.39 months for patients with lower thoracic tumors. Also, the four-year survival rate for patients with mid-thoracic tumors was 49%, and for patients with lower thoracic tumors, it was 44%. The log-rank test showed no significant association between overall survival and tumor location (P=0.412). Similarly, the mean overall survival of patients with tumor grades one, two and three were 35, 52, and 43 months, respectively. The four-year survival rate for patients with tumors of grade one, two and three were 40%, 48% and 62%, respectively. However, the log-rank test showed no significant association between overall survival and tumor grade (P=0.350).

Furthermore, the mean overall survival of patients with dysphagia grades one, two and three were 37, 50 and 53 months, respectively. The four-year survival rate for patients with dysphagia grades one, two and three were 25%, 51% and 55%, respectively. However, the log-rank test showed no significant association between overall survival and dysphagia grade (P=0.907).

3.6.2. The patients' overall survival and functional index

The mean overall survival of patients with a functional index less than 2 was 52 months, while it was 43 months in patients with a functional index greater than or equal to 2. In patients with functional index less than 2, the four-year survival rate was 50% but it was 32% in those with functional index greater than or equal to 2. However, the result of the log rank test showed no significant association between the overall survival of the patients and the functional index (P=0.832).

3.6.3. The patients' overall survival and side effects

The mean overall survival of patients with and without side effects in the course of treatment were 50 and 55 months, respectively. In addition, the four-year survival rates for patients with and without side effects were 50% and 49%, respectively. However, the log-rank test showed no significant association between overall survival and side effects (P=0.273).

3.6.4. The patients' overall survival and clinical response to treatment

Also, the mean overall survival of patients with a complete and incomplete clinical response were 55 and 24 months,

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respectively. In Addition, the four-year survival rate for patients with a complete and incomplete clinical response were 55% and 26%, respectively. The log-rank test showed a significant association between overall survival and clinical response (P=0.003).

3.6.5. The patients' overall survival and chemotherapy regimens

The mean overall survival of patients with 5 sessions of chemotherapy with regimen (PACI+CARBO)-TC REGIME was 57 months, while it was 30 months for patients with 2 sessions of chemotherapy with regimen (CIS+5FU) and 29 months for patients 5 sessions of chemotherapy with regimen (CIS+IRINO). The four-year survival rate in patients with 5 sessions of chemotherapy with regimen (PACI+CARBO-TC) was 53% while its was 22% in patients with 2 sessions of chemotherapy with regimen (CIS+5FU) and 30% for those with 5 sessions of chemotherapy with regimen (CIS +IRINO). The log-rank test results showed a significant association between overall survival and chemotherapy (P=0.034).

3.6.6. The patients' overall survival and radiation doses

Also, the mean overall survival of patients with one to four brachytherapy sessions with a dose of 5 Gray were 28, 45, 39, and 20 months, respectively. The four-year survival rate for patients with two and three brachytherapy sessions with a dose of 5 Gray was 61% and 35%, respectively. The log-rank test showed a significant association between overall survival and brachytherapy dose, and patients receiving a dose of 10 Gray had better survival compared to those receiving a 15 Gray dose (P=0.006). Also, the mean overall survival of patients with a radiotherapy dose of 45-49.9 Gray was 40 months, while it was 49 months for patients with a radiotherapy dose of more than 50 Gray. The four-year survival rate of patients with a radiation dose of 45-49.9 and more than 50 Gray were 34% and 57%, respectively. The result of the log-rank test showed a significant association between overall survival and radiotherapy dose (P=0.036).

3.6.7. The patients' overall survival and local and distant recurrence

The mean overall survival of patients with and without local recurrence were 27 and 64 months, respectively. The four-year survival rate of patients with local recurrence was 26%, and for patients without local recurrence, it was 62%. The result of the log rank test showed a significant association between overall survival and local recurrence (P<0.001). In addition, the mean overall survival of patients with and without local or distant recurrence were 26 and 83 months, respectively. The four-year survival rate for patients with and without local or distant recurrence was 18% 90%, respectively. The result of the log-rank test showed a significant association between overall survival and local or distant recurrence (P<0.001).

3.6.8. Factors associated with the overall survival

In order to examine the independent factors associated with the overall survival, variables such as age, ECOG, CCR, Total.dose.ebrt, Total.dose.BRT, Side.effect, Mets, tumor size, tumor recurrence and chemotherapy regimen were entered into the Cox regression model; the results showed that the independent variable associated with overall survival included the local or distant recurrence involvement. Therefore, it can be concluded that the risk ratio of death in individuals with local or distant recurrence compared to those without recurrence is approximately 11 times (P>0.001) (**Table 5**).

Table 5. Results of Cox regression to determine independent factors associated with overall survival

Variables	Model coefficient	Risk ratio	Confidence interval 95%	P- value
CCR	-0.191	0.8260	(0.426,1.601)	0.571
(PACI+CARBO) (5 sessions)				0.681
(CIS+IRINO) (5 sessions)	0.029	1.029	(0.287,3.687)	0.965
(CIS+5FU) (2 sessions)	-0.255	0.775	(0.234,2.566)	0.676
Total.dose.ebrt	0.343	1.409	(0.794,2.500)	0.241
Local.Distant.Cat	2.422	11.263	(4.293,29.555)	0.000

3.7. The patients' disease-free interval

3.7.1. The patients' disease-free interval and tumor location and size

The mean disease-free interval of patients with mid-thoracic and lower thoracic tumors were 35.54 and 48.53 months, respectively. The four-year disease-free interval rate for patients with mid-thoracic and lower thoracic tumors were 36% and 46%, respectively. However, the log-rank test showed no significant association between disease-free interval and tumor location (P=0.353). Moreover, the mean disease-free interval for patients with tumors of grade one, two and three were 29, 45 and 22 months, respectively. The four-year disease-free interval rate for patients with tumors of grade one, and two were 35%, 44%, respectively. But the log-rank test showed no significant association between disease-free interval and tumor grade (P=0.651).

3.7.2. The patients' disease-free interval and functional index

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The mean disease-free interval of patients with a functional index less than two was 43 months, while it was 34 months for patients with a functional index greater than or equal to two. The four-year survival rate for patients with a functional index less than two was 41%, but it was 36% for patients with a functional index greater than or equal to two. However, the log-rank test showed no significant association between disease-free interval and functional index (p=0.739).

3.7.3. The patients' disease-free interval and dysphagia grade

The mean disease-free interval for patients with dysphagia grade one, two and three were 35, 43 and 41 months, respectively. The four-year survival rate for patients with dysphagia grade one, two and three were 34%, 48% and 39%, respectively. But the log-rank test showed no significant association between disease-free interval and dysphagia grade (P=0.905).

3.7.4. The patients' disease-free interval and side effects

The mean disease-free interval for patients with and without side effects during treatment were 37 and 54 months, respectively. The four-year survival rate for patients with and without side effects were 34% and 54%, respectively. The results of the log-rank test showed a significant association between disease-free interval and side effects (P=0.013).

3.7.5. The patients' disease-free interval and clinical response to treatment

The mean disease-free interval for patients with complete and incomplete clinical response were 48 and 8 months, respectively. The four-year survival rate in patients with a complete clinical response was 47%. The results of the log-rank test showed a significant association between disease-free interval and clinical response (p<0.001).

3.7.6. The patients' disease-free interval and chemotherapy regimens

The mean disease-free interval of patients with 5 sessions of chemotherapy with regimen (PACI+CARBO-TC) was 46 months; it was 24 months for patients with 2 sessions of chemotherapy with regimen (CIS+5FU) and 26 months for those with 5 sessions of chemotherapy with regimen (CIS+) IRINO). The four-year survival rate in patients with 5 sessions of chemotherapy with (PACI+CARBO)-TC regimen was 44% while it was 19% in patients with 2 sessions of chemotherapy with regimen (CIS+5FU). However, the log rank test showed no significant association between disease-free interval and chemotherapy (p=0.087).

3.7.7. The patients' disease-free interval and brachytherapy dose

The number of patients who experienced recurrence after one to four brachytherapy sessions were 0, 27, 27, and 4, respectively. Also, the four-year survival rate for patients with two and three brachytherapy sessions with a dose of 5 Gray was 44% and 32%, respectively. But the results of the log-rank test showed no significant association between disease-free interval and brachytherapy dose (p=0.088).

3.7.8. The patients' disease-free interval and radiotherapy dose

The mean disease-free interval for patients with radiotherapy doses of 45-49.9 and more than 50 Gray were 37 and 39 months, respectively. The four-year survival rate for patients with radiotherapy doses of 45-49.9 and more than 50 Gray were 32% and 42%, respectively. However, the results of the log-rank test showed no significant association between disease-free interval and radiotherapy dose (P=0.337).

3.7.9. Factors associated with the disease-free interval of survival

Also, in order to examine the independent factors associated with disease-free interval, the variables of age, ECOG, CCR, total dose EBRT, total dose BRT, side effect, tumor size, tumor recurrence and chemotherapy regimen were entered into the cox regression model; and the results showed that the independent variable associated with disease-free interval was the complete clinical response to treatment. The risk ratio of recurrence in individuals with a complete clinical response to those with an incomplete clinical response was approximately 0.33. (P=0.001) (Table 6).

4. DISCUSSION

The present study aimed to determine the rate of complications and treatment outcomes following intraluminal brachytherapy after definitive chemoradiation in patients with esophageal cancer. Definitive chemoradiotherapy (dCRT) is widely considered as a treatment option for cervical esophageal carcinoma. It is reported that this treatment have an acceptable response rate and short-term survival of dCRT concomitant with docetaxel, 5-fluorouracil (DCF-RT), and cisplatin for advanced cervical esophageal squamous cell carcinoma (ESCC) patients (18). Due to the development of tracheoesophageal fistulas caused by brachytherapy in

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Table 6. Results of Cox regression to determine independent factors associated with disease-free interval

Variables	Model coefficient	Risk ratio	Confidence interval 95%	Probability value
CCR	-1.053	0.349	(0.189 ,0.645)	0.001
(PACI+CARBO) (5 sessions)				0.142
(CIS+IRINO) (5 sessions)	-.340	0.712	(0.218 ,2.321)	0.573
(CIS+5FU) (2 sessions)	0.253	1.288	(0.365 ,4.542)	0.694
Side.effect.cat	-0.723	0.485	(0.233 ,1.010)	0.053

patients with cervical esophageal cancer, we excluded these patients from our study. Our findings demonstrated minimal complications when applicators with a diameter of 6–10 mm were used. This outcome aligns with the study by Nishimura et al. (19), which also reported no mortality or esophageal fistulas. However, unlike our study, the applicators used in Nishimura's research were larger, ranging from 10 to 20 mm in diameter.

Although HDR brachytherapy protocols in other studies have shown significant heterogeneity—particularly in applicator dimensions, treatment depths, and dose regimens—our approach was guided by the ABS guidelines (20). According to these recommendations, ideal candidates for endoluminal HDR brachytherapy are patients with primary tumors measuring ≤10 cm, confined to the esophageal wall, limited to the thoracic esophagus, and without systemic metastases. Patients who do not meet these criteria are considered poor candidates for this treatment. Specifically, brachytherapy is contraindicated in cases of esophageal fistulas, cervical esophageal involvement, or impassable strictures.

In this study, the distribution of male and female patients was approximately equal. The highest overall survival (OS) and disease-free interval (DFI) were reported as 47.26 months and 22.62 months, respectively. In a similar study involving patients with esophageal cancer treated with intraluminal brachytherapy following definitive chemoradiotherapy, the mean DFI was 13.8 months, ranging from 0 to 27 months (21).

While 61% of patients in the comparative study experienced local recurrence, our findings showed that nearly 68% of patients were free from local recurrence, and approximately 47% had no recurrence of any kind (local or distant). A significant correlation was identified between recurrence (local or distant) and overall survival ($P < 0.001$). Patients with local or distant recurrence had an approximately 11-fold higher risk of death compared to those without recurrence ($P < 0.001$).

In the study by Mangesius et al. (22), which compared concurrent chemoradiotherapy with and without brachytherapy, the brachytherapy dose was 10 Gy delivered in two sessions one week apart. The study concluded that both the mean progression-free interval and overall survival were significantly improved in the brachytherapy group ($P < 0.0001$).

No significant difference was observed in the overall rate of acute toxicity between the two groups. However, the incidence of acute esophagitis was significantly higher in the brachytherapy group. Despite this, there was no difference in the occurrence of fatal late toxicities.

The mid-thoracic esophagus was the most commonly affected area, involving 60 patients (48%). Tumor location showed no significant impact on OS or DFI ($P = 0.54$), consistent with findings by Sharan et al., who also found no link between tumor location and disease-free intervals.

In the retrospective study by Sharan et al. (21), the medical records of 26 eligible patients with non-metastatic esophageal carcinoma treated with definitive chemoradiotherapy followed by intraluminal brachytherapy between 2008 and 2011 were analyzed. The radiotherapy method in their study was similar to ours, following standard protocols. However, in our study, different chemotherapy regimens were used concurrently with radiotherapy, while in their study, patients received external beam radiotherapy with weekly cisplatin at 40 mg/m^2 for a total of six cycles.

In our analysis, 93 patients received radiotherapy doses ≥50 Gy, which resulted in significantly higher mean OS compared to patients who received doses <50 Gy ($P = 0.036$). However, no significant association was observed between radiotherapy dose and DFI ($P > 0.05$).

In contrast, a phase III multicenter randomized trial (NROG-001) reported no improvement in OS for patients receiving high-dose radiotherapy (59.4 Gy) compared to the standard-dose group (50.4 Gy) ($P = 0.54$). However, an improvement in progression-free interval (PFS) was noted in the high-dose group.

In a 2014 study, 218 patients were included after an interim analysis. It was found that the high-dose arm (64.8 Gy) was unlikely to provide better survival compared to the standard-dose arm. No significant differences were observed in median survival time, two-year survival rates, or local control between the high-dose and standard-dose groups. However, there were 11 treatment-related deaths in the high-dose group compared to only two in the standard-dose group, indicating a higher mortality risk with increased doses. Based on these results, the standard dose of 50.4 Gy remains valid. The study concluded that increasing the dose beyond

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50.4 Gy does not improve patient outcomes and is associated with greater cardiovascular and pulmonary complications in the external radiotherapy group, which are expected to be lower with brachytherapy (23).

Among 125 patients, 106 achieved a complete clinical response to treatment, which was significantly associated with overall survival ($P < 0.003$).

In the study by Murakami et al. (24), 87 patients with thoracic esophageal cancer (T1N0M0) were treated with brachytherapy following radiotherapy between 1992 and 2002. Of the 44 patients with mucosal involvement, 43 achieved a complete clinical response, and among 41 patients with submucosal involvement, 40 achieved a complete response. This higher response rate may be attributed to the inclusion criteria (T1N0M0) in their study, while deeper tumor involvement was included in ours. Approximately 93% of their patients received brachytherapy doses of 10–15 Gy, showing a significant correlation between brachytherapy dose and overall survival ($P = 0.006$), though no significant correlation was observed with disease-free interval ($P > 0.05$).

In the study by Mingyue et al. (25), 32 patients with early-stage esophageal cancer underwent radiotherapy alone (total dose: 60 Gy), and another 32 received combined brachytherapy and radiotherapy (RT dose: 50 Gy; 2 Gy/session, 5 days/week; brachytherapy dose: 10 Gy, 5 Gy/session weekly). Local control rates at 1, 2, and 3 years post-treatment were higher in the brachytherapy + RT group (88%, 72%, and 53%) compared to the RT-alone group (22%, 25%, and 9%). Similarly, three-year overall survival rates were 38% and 9%, respectively. This study, like ours, concluded that brachytherapy combined with radiotherapy significantly improves overall survival ($P = 0.04$). Additionally, it found that mid-esophageal tumors had a poorer prognosis ($P = 0.03$).

Gaspar et al. conducted a prospective study on patients with unresectable esophageal cancer. These patients were initially treated with external beam radiotherapy (50 Gy) combined with concurrent chemotherapy. After a 2-week rest period, they underwent brachytherapy as part of their treatment. Patients received either 15 Gy (HDR, 5 Gy/week for 3 weeks) or 20 Gy (LDR, single fraction). Median survival was 11 months, with local recurrence in 63% of HDR-treated patients. Six patients developed esophageal fistulas, leading to three deaths, highlighting the need for caution with brachytherapy, especially when combined with chemotherapy. These findings differ from ours, where the median survival was 47.26 months, and local recurrence occurred in only 32% of patients. This discrepancy may stem from differences in treatment timing, as our patients underwent brachytherapy following definitive chemoradiotherapy, and all were treated with HDR techniques (26).

A meta-analysis of prospective studies involving 623 patients concluded that brachytherapy is a highly effective and relatively safe treatment option, though underutilized. Severe complications occurred in 23% of cases, including esophageal strictures (12%) and esophagotracheal fistulas (8%). Other studies have shown that HDR brachytherapy effectively alleviates dysphagia in 90% of patients (27). In our study, severe complications occurred in 16% of patients, including esophageal strictures (8.8%), odynophagia (5.6%), and grade 2 and 3 dysphagia (17.6% and 6.6%, respectively). Our study concluded that intraluminal brachytherapy as a boost following concurrent chemoradiotherapy is well-tolerated and has the potential to improve outcomes. However, further studies are required to define its role in definitive treatment.

5. CONCLUSION

As the strength of the present study, it can be considered as the first study on the effect of intraluminal brachytherapy after definitive chemoradiation in patients with esophageal cancer in Iran, and the results are consistent with similar studies. According to the findings, intraluminal brachytherapy after definitive chemoradiation in patients with esophageal cancer was found to be effective and the effect of this treatment modality was considerable in changing the treatment management of patients; therefore we would like to recommended this treatment for clinical use; however, there is a need for more supplementary studies with a larger sample size for the routine use of this therapeutic modality. Also, this study was the first of its kind in our country, it can still be a valuable guide for motivated radiation oncologists to consider intraluminal brachytherapy as an effective treatment option for patients with esophageal cancer.

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Conflict of interest

There is no conflict of interest regarding this project.

Ethical statement

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The principles of confidentiality, ethics, and anonymization of personal identities and information were strictly adhered during the study. Also, this research was presented to the Ethics Committee of Mashhad University of Medical Sciences, Iran in 2021, and was approved by the committee (Ethics Code: IR.MUMS.IRH.REC.1401.019).

References

1. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. The Lancet. 2013;381(9864):400-12.
2. Safaei AM, Ghalehtaki R, Khanjani N, Farazmand B, Babaei M, Esmati E. High-dose-rate intraluminal brachytherapy prior to external radiochemotherapy in locally advanced esophageal cancer: preliminary results. Journal of Contemporary Brachytherapy. 2017;9(1):30-5.
3. Jayaprakash S, Hegde M, Girisa S, Alqahtani MS, Abbas M, Lee EH, Yap KC, Sethi G, Kumar AP, Kunnumakkara AB. Demystifying the functional role of nuclear receptors in esophageal cancer. International Journal of Molecular Sciences. 2022 Sep 19;23(18):10952.
4. https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/survival
5. Bhatt L, Tirmazy S, Sothi S. Intraluminal High Dose Rate Brachytherapy for Palliation of Dysphagia in Cancer of the Oesophagus. Clinical Oncology. 2011;23(3):S30.
6. Sjödahl K, Lu Y, Nilsen TI, Ye W, Hveem K, Vatten L, et al. Smoking and alcohol drinking in relation to risk of gastric cancer: a population-based, prospective cohort study. International journal of cancer. 2007;120(1):128-32.
7. Lagergren J, Bergström R, Nyrén O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Annals of internal medicine. 1999;130(11):883-90.
8. Ding G-C, Ren J-L, Chang F-B, Li J-L, Yuan L, Song X, et al. Human papillomavirus DNA and P16INK4A expression in concurrent esophageal and gastric cardia cancers. World journal of gastroenterology: WJG. 2010;16(46):5901.
9. Kamath A, Wu T-T, Heitmiller R, Daniel R, Shah K. Investigation of the association of esophageal carcinoma with human papillomaviruses. Diseases of the Esophagus. 2000;13(2):122-4.
10. Ponvilawan B, Rittiphairoj T, Charoenngam N, Rujirachun P, Wattanachayakul P, Tornsatitkul S, et al. Association between Chronic Hepatitis C Virus Infection and Esophageal Cancer: A Systematic Review and Meta-Analysis. Journal of Clinical Gastroenterology. 2022;56(1):55-63.
11. Chen T, Cheng H, Chen X, Yuan Z, Yang X, Zhuang M, et al. Family history of esophageal cancer increases the risk of esophageal squamous cell carcinoma. Scientific reports. 2015;5(1):1-9.
12. Sharma P, Jain S, Karunanithi S, Pal S, Julka PK, Thulkar S, et al. Diagnostic accuracy of 18 F-FDG PET/CT for detection of suspected recurrence in patients with oesophageal carcinoma. European journal of nuclear medicine and molecular imaging. 2014;41:1084-92.
13. Surasi DS, Bhambhvani P, Baldwin JA, Almodovar SE, O'Malley JP. 18F-FDG PET and PET/CT patient preparation: a review of the literature. Journal of nuclear medicine technology. 2014;42(1):5-13.
14. Kleinberg L, Brock M, Gibson M. Management of locally advanced adenocarcinoma of the esophagus and gastroesophageal junction: finally a consensus. Current treatment options in oncology. 2015;16:1-16.
15. Yorozu A, Dokiya T. Brachytherapy for esophageal cancer: optimum dose and indications in the modern era. Brachytherapy: Techniques and Evidences. 2019:283-300.
16. Scarpa M, Valente S, Alfieri R, Cagol M, Diamantis G, Ancona E, et al. Systematic review of health-related quality of life after esophagectomy for esophageal cancer. World journal of gastroenterology: WJG. 2011;17(42):4660.
17. Folkert MR, Gil'ad NC, Wu AJ, Gerdes H, Schattner MA, Markowitz AJ, et al. Endoluminal high-dose-rate brachytherapy for early stage and recurrent esophageal cancer in medically inoperable patients. Brachytherapy. 2013;12(5):463-70.
18. Okamoto H, Taniyama Y, Sato C, Fukutomi T, Ozawa Y, Ando R, et al. Definitive Chemoradiotherapy with Docetaxel, Cisplatin, and 5-Fluorouracil for Advanced Cervical Esophageal Cancer: A Medium-Term Outcome. Asian Pacific Journal of Cancer Prevention. 2022;23(2):495-9.
19. Nishimura Y, Okuno Y, Ono K, Mitsumori M, Nagata Y, Hiraoka M. External beam radiation therapy with or without high-dose-rate intraluminal brachytherapy for patients with superficial esophageal carcinoma. Cancer: Interdisciplinary International Journal of the American Cancer Society. 1999 Jul 15;86(2):220-8.
20. Gaspar LE, Nag S, Herskovic A, Mantravadi R, Speiser B. American Brachytherapy Society (ABS) consensus guidelines for brachytherapy of esophageal cancer. Clinical Research Committee, American Brachytherapy Society, Philadelphia, PA. International journal of radiation oncology, biology, physics. 1997;38(1):127-32.
21. Sharan K, Fernandes DJ, Prakash Saxena PU, Banerjee S, Sathian B. Treatment outcomes after intraluminal brachytherapy following definitive chemoradiotherapy in patients with esophageal cancer. J Cancer Res Ther. 2014;10(2):337-41.
22. Mangesius J, Hörmandinger K, Jäger R, Skvortsov S, Plankensteiner M, Maffei M, Seppi T, Dejaco D, Santer M, Sarcletti M, Ganswindt U. Chemoradiotherapy Combined with Brachytherapy for the Definitive Treatment of Esophageal Carcinoma. Cancers. 2023 Jul 12;15(14):3594.
23. Tai P, Yu E. Esophageal cancer management controversies: Radiation oncology point of view. World journal of gastrointestinal oncology. 2014;6(8):263.
24. Murakami Y, Nagata Y, Nishibuchi I, Kimura T, Kenjo M, Kaneyasu Y, Okabe T, Hashimoto Y, Akagi Y. Long-term outcomes of intraluminal brachytherapy in combination with external beam radiotherapy for superficial esophageal cancer. International journal of clinical oncology. 2012 Jun;17:263-71.
25. Ye M, Han D, Mao Z, Cheng G. A prospective study of radical external beam radiotherapy versus external beam radiotherapy combined with intraluminal brachytherapy for primary esophageal cancer. Brachytherapy. 2022 Sep 1;21(5):703-11.
26. Gaspar LE, Winter K, Kocha WI, Pinover WH, Graham M, Gunderson L. Swallowing function and weight change observed in a phase I/II study of external-beam radiation, brachytherapy and concurrent chemotherapy in localized cancer of the esophagus (RTOG 9207). Cancer Journal (Sudbury, Mass). 2001;7(5):388-94.
27. Fuccio L, Mandolesi D, Farioli A, Hassan C, Frazzoni L, Guido A, et al. Brachytherapy for the palliation of dysphagia owing to esophageal cancer: A systematic review and meta-analysis of prospective studies. Radiotherapy and Oncology. 2017;122(3):332-9.

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