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ORIGINAL ARTICLE

Soft-Tissue Metastases From Esophageal Cancer

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Abstract

Background Metastatic carcinoma to skeletal muscle and/or subcutaneous fat is a rare event. Only 27 cases of esophageal cancer to soft tissue have been described in the English-language literature.

Purpose Our goal was to describe the prevalence and clinical characteristics of soft-tissue metastasis among patients with primary esophageal cancer at a single institution.

Methods We performed a retrospective review of all patients with primary esophageal cancer. Data points analyzed included histologic subtype, anatomic location, metastasis pattern, treatment, and survival. Kaplan-Meier curves were used to estimate survival time, and log-rank tests were used for comparisons. For all analyses, $P < 0.05$ was considered significant.

Results Of 1341 patients with primary esophageal cancer, 25 (1.9%) had metastases to soft tissue. Soft-tissue metastases were diagnosed at a median age of 64 years, a median 9.6 months after esophageal cancer diagnosis. Adenocarcinoma was the predominant histopathological type, and soft-tissue metastasis was most common in the lower extremity. Local intervention was used for 10 symptomatic patients with favorable prognoses. Chemotherapy was the only treatment modality in 18 patients. Median survival time after diagnosis of soft-tissue metastasis was 8.9 months and was longer in patients with metastasis in soft tissue only (24.6 months, $P = 0.007$) and in those who received local intervention (11.1 months vs those who did not, $P = 0.020$).

Conclusion We estimate the prevalence of soft-tissue metastasis to be 1.9% among patients with esophageal cancer. Local intervention may be beneficial for patients in otherwise good health with symptomatic soft-tissue lesions.

Keywords Metastatic esophageal cancer · Soft tissue metastases

Introduction

Esophageal cancer is an aggressive disease associated with loco-regional and distant spread.[1] Prognosis depends greatly on local primary tumor invasion and the presence of distant metastases, which frequently occur in the liver, lungs, bones, adrenal glands, kidneys, and brain.[2] Metastatic disease carries a poor prognosis of survival of approximately 5% at 5 years.[1]

Metastatic esophageal cancer to soft tissue, defined as metastatic disease to skeletal muscle and/or subcutaneous fat, is rare, with only 27 cases[3–24] described in the English-language literature. Prevalence has not been well established; the largest single-center study reported only four cases of esophageal cancer with metastasis to skeletal muscle.[5] Treatment of soft-tissue metastasis from all types of malignant tumors is multidisciplinary, consisting of chemotherapy in cases of widespread metastases and local intervention in patients with symptomatic lesions and good performance status.[5,6, 22] With advances in oncologic treatment, the prognosis for cancer patients has improved, potentially shifting metastatic patterns of disease.

The purpose of our investigation was to describe the clinical characteristics of metastatic esophageal cancer to soft tissue. We sought to determine the prevalence of esophageal metastasis to soft tissue, the location of soft-tissue metastases, treatment types, and duration of survival. We aimed to

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determine the factors influencing the treatment and survival of patients with soft-tissue metastases from primary esophageal cancer.

Methods

Our study was approved by the Johns Hopkins institutional review board (IRB 00148197). We reviewed records of 1341 patients with esophageal cancer in our institution's cancer registry from January 1997 through July 2017. We included patients ≥ 17 years old with radiologically or histologically proven soft-tissue metastases. We excluded patients whose soft-tissue metastases were caused by a primary cancer other than esophageal cancer, as well as patients with bony metastases. Twenty-six patients with 41 soft-tissue lesions were included.

We extracted data on patient age, sex, esophageal cancer histology and location, dates of primary and metastasis diagnoses, pattern of metastasis, treatment modality, and date of death/last follow-up. Soft-tissue metastases were categorized as occurring in the upper extremity, lower extremity, or trunk. Imaging studies, including computed tomography (CT) scans, positron emission tomography (PET)-CT, and magnetic resonance imaging (MRI), were reviewed for each patient. Pathology reports were reviewed if available.

Survival analysis was performed using Kaplan-Meier curves, describing survival times from diagnoses of esophageal cancer and soft-tissue metastasis. Mantel-Cox univariate analysis was used to determine the associations of widespread metastases, extent of soft-tissue involvement, and systemic and local treatment with survival time. For all analyses, $P < 0.05$ was considered significant.

Results

Demographic Characteristics

Of the 1341 patients with primary esophageal cancer, 25 (1.9%) had metastases to soft tissue. One other patient in our series was seen on a consultation basis and did not receive treatment at our institution; therefore, the patient was excluded from the prevalence calculation.

Of the 26 patients in our study, 6 were women (23%). Most patients (92.3%) did not have metastatic disease at the time of esophageal cancer diagnosis. Esophageal cancer diagnoses were staged as follows: stage II, 4 patients; stage III, 14 patients; and (metastatic) stage IV, 8 patients (2 of whom had soft-tissue metastases). Soft-tissue metastases were diagnosed at a median age of 64 years (range 38–84) and a median 9.6 months (range 0–47.9) after esophageal cancer diagnosis. Adenocarcinoma was the most common histologic subtype ($n = 22$), followed by squamous cell carcinoma ($n = 4$). The cancer affected the distal one third of the esophagus in 25 patients (Table 1).

Skeletal muscle was the most common site of soft-tissue metastasis (Figs. 1 and 2). Nineteen patients had isolated muscular metastases, and 5 had both muscular and subcutaneous fat lesions. Only 2 patients had isolated subcutaneous fat metastases (Table 2). Although 15 patients had a single soft-tissue metastatic lesion, a total of 41 sites of soft-tissue metastases were observed. Of these 41 sites, the most common was the lower extremity ($n = 17$), followed by the trunk ($n = 14$) and upper extremity ($n = 10$). Though the number of patients with squamous cell carcinoma to soft tissue was small, there were a few noticeable differences between the squamous cell and adenocarcinoma groups. Soft tissue metastatic squamous cell carcinoma was more often multifocal ($n = 2/4$) when compared to patients with adenocarcinoma ($n = 8/22$). In addition, squamous cell preferentially affected the extremities over the trunk. Fourteen patients were asymptomatic at the site of the soft-tissue lesion, with the tumors discovered as incidental findings on surveillance imaging. Three patients had soft-tissue metastases as the only site of disease (Table 2).

Treatment

Treatment information was available for 24 patients (2 patients were lost to follow-up). Systemic chemotherapy was the predominant treatment modality ($n = 18$) and was the only therapeutic intervention in 12 patients. Of those who did not receive systemic chemotherapy, 4 patients received local treatment and 2 patients received hospice care. Ten patients received local treatment to the metastatic focus with or without systemic therapy. The most common local interventions were radiation only ($n = 4$) or a combination of radiation and surgical resection ($n = 4$), followed by surgical resection only ($n = 2$) (Table 3). Surgical excision was indicated in 2 patients as a curative treatment for focal metastases to soft tissue only. On follow-up, of the 10 patients considered for local intervention, 4 reported improvement in pain and 4 had complete resolution of pain. The remaining 2 patients reported no improvement in pain. Of the patients diagnosed with stage-IV esophageal cancer, 4 patients (50%) received local intervention for soft-tissue metastases. Neither of the 2 patients who had soft-tissue metastases at initial presentation received local intervention.

Survival Analysis

Median survival time after primary diagnosis was 24.3 months. Median survival time after diagnosis of soft-tissue metastasis was 8.9 months (Table 4 and Fig. 3). Univariate analysis showed significantly shorter median survival times in patients with widespread disease

Table 1 Characteristics of 26 patients diagnosed with metastatic esophageal cancer

Characteristics	*N* (%)
Age at soft-tissue metastasis diagnosis (years)	64 (38–84)[a]
Time to soft-tissue metastasis diagnosis after primary cancer diagnosis (months)	9.6 (4.4–14.7)[b]
Female sex	6 (23)
Primary histological subtype	
Adenocarcinoma	22 (85)
Squamous cell carcinoma	4 (15)
Primary anatomic esophageal location	
Proximal	0 (0.0)
Middle	1 (3.8)
Distal	25 (96)
Cancer stage at diagnosis	
II	4 (15.4)
III	14 (53.8)
IV	8 (30.8)

[a] Data presented as median (range)

[b] Data presented as median (95% confidence interval)

involving visceral organs or bone (5.2 months, $P = 0.007$), those with soft-tissue metastases to subcutaneous fat only without muscle involvement (1.3 months, $P = 0.001$), and those not receiving local treatment for soft-tissue metastases (4.6 months, $P = 0.020$). Patients who did not receive local radiation therapy had a significantly shorter median survival time (5.2 months) than those who did (13.3 months) ($P = 0.007$) (Table 4 and Fig. 4). Histologic type, metastatic pattern, metastasis at initial diagnosis, location of metastasis, metastasis to muscle, and use of chemotherapy were not associated with differences in survival duration.

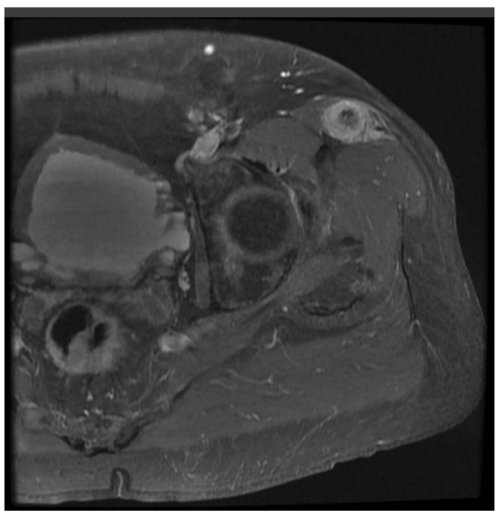

Fig. 1 Axial fat-suppressed T2-weighted magnetic resonance image showing a 2.2 × 1.8-cm mass in the left sartorius muscle

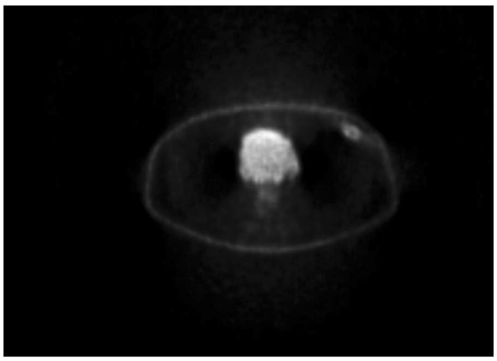

Fig. 2 Positron emission tomography scan showing an area of high standardized uptake values (SUV) consistent with a soft-tissue metastasis

Discussion

Metastatic disease to soft-tissue sites is rare,[22,23,25–28] which has been attributed to local soft-tissue pH and temperature, and accumulation of metabolites. It is the general consensus that tumor dissemination to soft tissue is hematogenous.[23,26] Whereas other more common sites of metastases receive constant blood flow, skeletal muscle receives variable blood flow controlled by B-adrenergic receptors, leading to varying tissue pressures.[22] In addition, the frequent movement of muscle and associated lactic acid production may create a difficult site for implantation for intramuscular metastases.[28]

Table 2 Clinical characteristics of 41 soft-tissue metastases from esophageal cancer in 26 patients

Characteristics	*N* (%)
Lesion location	
Upper extremity	10 (24)[a]
Lower extremity	17 (41)[a]
Trunk	14 (34)[a]
Soft-tissue subtype	
Muscle	19 (73)[b]
Subcutaneous fat	2 (7.7)[b]
Both	5 (19)[b]
Burden of disease	
Widespread	23 (88)[b]
Soft-tissue metastasis only	3 (12)[b]
Symptomatic soft-tissue lesion	
Yes	12 (46)[b]
No	14 (54)[b]
Soft-tissue metastases	
Solitary	15 (58)[b]
Multiple	11 (42)[b]

[a] Refers to number (%) of lesions

[b] Refers to number (%) of patients

Table 3 Treatment types for 24 patients with soft-tissue metastases from esophageal cancer

Treatment type	*N* (%)
Chemotherapy	18 (75)
Chemotherapy only	12 (50)
Local therapy	
Radiation only	4 (17)
Surgical resection only	2 (8.3)
Radiation and surgical resection	4 (17)
None	2 (8.3)

Data available from 24 of 26 patients because 2 patients were lost to follow-up

Because the esophagus lacks serosa, esophageal cancer has the potential to invade adjacent structures in the neck and thorax,[29] as well as to disseminate distantly.[2] Few cases of metastatic esophageal cancer to soft tissue have been described.[3–24] Therefore, prevalence has not been well established, with few single-center studies reported.[5,15] In 2012, Cincibuch et al.[5] reported the largest single-institution experience. They found 4 cases of skeletal muscle metastasis among 205 patients with esophageal cancer, estimating the prevalence at 2%. Nguyen et al.[15] reported on 13 patients with esophageal cancer and found 1 patient with soft-tissue metastasis. We estimate the prevalence of soft-tissue metastasis from esophageal cancer to be 1.9% overall and 1.7% for isolated skeletal muscle metastases. These estimates are similar to that of Cincibuch et al.[5] however, it is difficult to compare our study with that of Cincibuch et al. because of the large discrepancies in sample size (1341 vs 205, respectively) and number of patients with skeletal muscle metastases (23 vs 4, respectively).

When analyzing skeletal muscle metastases from all solid malignant tumors, Surov et al.[30] found a prevalence of 1.2% in 5170 patients with metastatic cancers. The primary malignancies associated with the highest prevalence of skeletal muscle metastasis were cervical carcinoma (4.9%), melanoma (3.6%), ovarian carcinoma (3.5%), and renal carcinoma (3.2%). The authors estimated that the prevalence of skeletal muscle metastasis among patients with esophageal cancer was 1.6%, without referencing how many cases were reviewed. Our series suggests that skeletal muscle metastasis from esophageal cancer occurs frequently (1.9%).

When extrapolating from data in the literature, we found that soft-tissue metastases were diagnosed at a median age of 58 years (range 42–77) and 0.38 months (range 0–54) after primary esophageal cancer diagnosis, with a large proportion (13/27, 48%) having soft-tissue metastases at initial diagnosis.[3,5–7,11–14,16–18,20–22,24] Compared with our series, patients reported that other studies were diagnosed with esophageal cancer at a younger age and developed metastases to soft tissue earlier in the disease course.

Table 4 Survival time after soft-tissue metastasis diagnosis in 26 patients with esophageal cancer

Parameter	Survival (months)		*P* value
	Median (SE)	95% CI	
Overall	8.9 (4.5)	0.2–17.6	NA
Sex			
Male	6.5 (2.5)	1.7–11.4	0.494
Female	11.5 (4.5)	2.8–20.2	
Histological type			
Adenocarcinoma	8.9 (4.1)	1.0–16.8	0.533
Squamous cell carcinoma	6.5 (4.6)	0.0–15.7	
Metastatic pattern			
Soft-tissue metastases only	24.6 (−)		0.007
Widespread metastases	5.2 (2.1)	1.1–9.3	
Metastases at initial cancer diagnosis			
No	8.9 (3.7)	1.7–16.0	0.389
Yes	5.2 (4.3)	0.0–13.5	
Number of soft-tissue lesions			
Single	8.9 (3.4)	2.2–15.6	0.852
Multiple	5.1 (0.7)	3.7–6.6	
Muscle metastases			
No	1.3 (−)		0.001
Yes	11.1 (3.5)	4.2–17.9	
Subcutaneous fat metastases			
No	8.9 (3.7)	1.7–16.1	0.828
Yes	2 (6.6)	0–14.9	
Upper extremity metastases			
No	11.1 (5.7)	0.1–22	0.945
Yes	6.5 (2.0)	2.7–10.4	
Lower extremity metastases			
No	6.5 (2.0)	2.7–10.4	0.856
Yes	11.1 (4.2)	2.7–19.4	
Trunk metastases			
No	11.4 (1.4)	8.6–14.2	0.120
Yes	2.6 (1.5)	0.0–5.5	
Chemotherapy			
No	2.1 (2.3)	0.0–6.5	0.421
Yes	8.9 (4.0)	1.0–16.8	
Radiation			
No	5.2 (1.6)	2.1–8.3	0.007
Yes	13.3 (2.8)	7.8–18.6	
Surgery			
No	6.5 (4.2)	0.0–14.7	0.130
Yes	8.9 (4.9)	0.0–18.6	
Local intervention			
No	4.6 (1.8)	1.1–8.2	0.020
Yes	11.1 (3.1)	5.0–17.1	

CI confidence interval, SE standard error

In our series, soft-tissue metastases from adenocarcinoma (85%) were far more common than those from squamous cell carcinoma (15%). Similar findings are reported in the literature, with most case reports (19/27, 70%) of soft-tissue

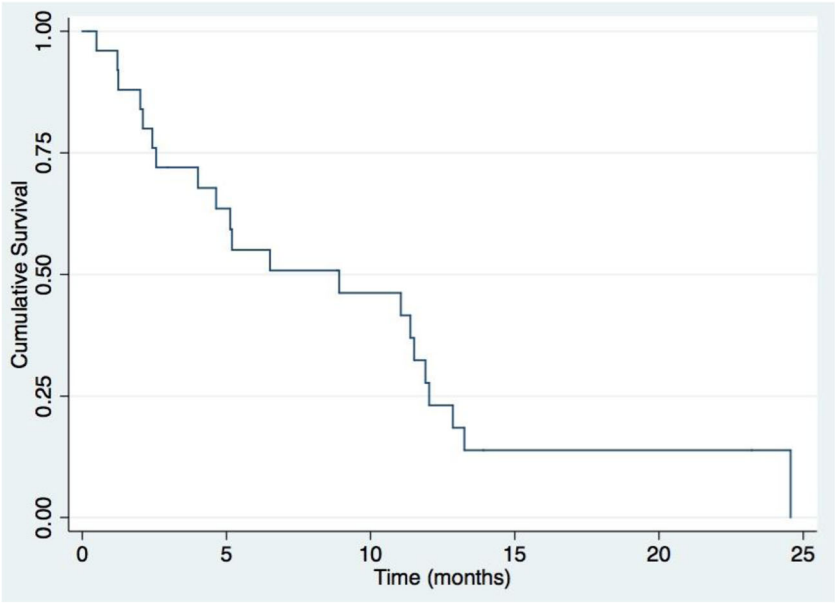

Fig. 3 Survival time of 26 patients after soft-tissue metastasis diagnosis (median, 8.9 months)

metastasis from esophageal cancer reported as adenocarcinoma.[3–24] This is likely attributable to the higher overall prevalence of primary adenocarcinoma, which typically affects the lower one third of the esophagus, as seen in 96% of the patients in our study and 83% (19/23) of cases in the literature. Esophageal metastasis to skeletal muscle is more common than metastasis to subcutaneous fat. We found that 73% of patients had isolated muscular metastases, whereas 19% had both muscular and subcutaneous fat lesions, and 7.7% had isolated subcutaneous fat lesions. This is consistent with previous studies in which 89% (24/27) of cases had skeletal muscle metastases and 11% (3/27) had metastases to subcutaneous fat. No soft-tissue metastases located in fatty sites deep to the fascia were reported.[3–24] Metastatic lesions occurred most commonly in the lower extremity in our study (42%) and in previous studies (70%). Similar proportions were observed for the upper extremity (24% vs 33%) and trunk (34% vs 30%).[3–24]

Soft-tissue metastases are typically not considered unless the patient develops pain or a palpable mass.[22] Asymptomatic soft-tissue metastases are often not diagnosed and are only discovered at autopsy.[25,31] In recent years, PET/CT has become widely utilized for pre-therapeutic staging of esophageal cancer because of its ability to detect distant metastases often not detected on other imaging modalities.[16,22,32–35] This could be one factor explaining the increase in reports of asymptomatic soft-tissue metastases.[5] In our series, 46% of patients had asymptomatic soft-tissue metastases detected on routine

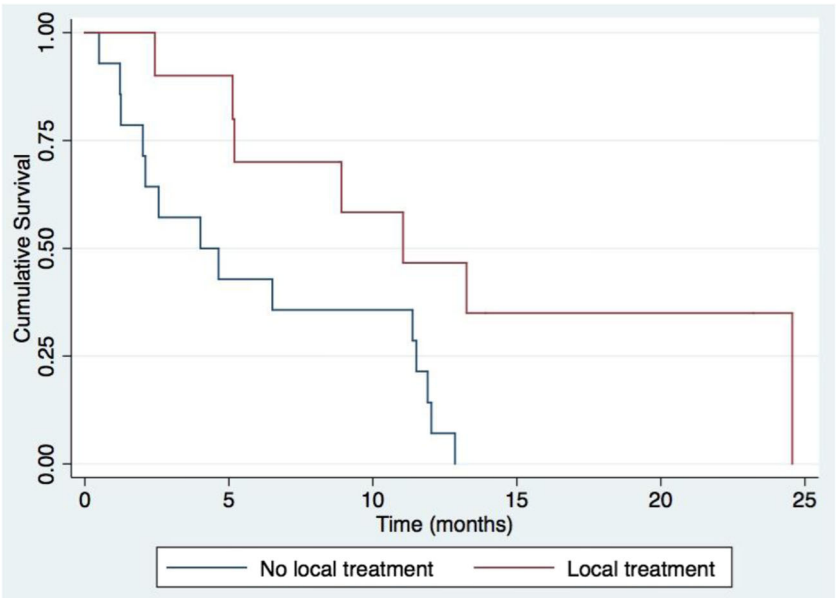

Fig. 4 Survival time after diagnosis of soft-tissue metastasis: local radiation therapy vs no local radiation therapy

imaging. Most asymptomatic lesions in our series were detected on PET/CT (62%), one of which was originally not detected on a CT scan (Fig. 2). In previous studies, 48% of patients (13/27) were asymptomatic at the location of soft-tissue metastasis, and all were diagnosed using PET/CT.[5,7,9,11,13,18,19,21,22] In our series, 3 patients underwent MRI to assess painful lesions, which showed the pathology. No diagnostic imaging study is able to accurately differentiate metastatic carcinoma from other cancers, and tissue biopsy is necessary to establish definitive histologic diagnosis when clinically indicated.[26] Ten patients in our cohort had histologically proven esophageal metastases to soft tissue.

Treatment of patients with metastatic soft-tissue disease is highly varied and depends on patient prognosis and symptoms. Guidelines for treatment of soft-tissue metastases recommend chemotherapy as monotherapy in patients with widespread metastases who are in good general condition.[5] Because soft-tissue metastases usually do not result in functional impairment or pose an immediate mortality risk, the general consensus is that local intervention should be restricted to symptomatic patients with a favorable prognosis.[5,6,22] Radiation therapy has been recommended for use in patients with symptomatic disease, whereas resection has been recommended in surgical candidates with symptomatic, localized disease only.[6] No guidelines have been established for the treatment of soft-tissue metastases from a primary esophageal cancer.

Treatment data for soft-tissue metastases from esophageal cancer in the literature show that most patients (16/19) received systemic chemotherapy, most of whom also underwent local therapy (12/19). Ten patients underwent localized radiation, and 3 had surgical resection of their soft-tissue metastatic lesions.[4–8,11,12,14,16–18,20–22] It is difficult to compare treatment data between our cohort and previous studies because or missing details about the burden of disease and symptoms. Burden of disease, functional impairment, and prognosis should be assessed when formulating a treatment plan. In our series, the median survival times after soft-tissue lesion diagnosis were 11.1 months for patients who received local treatment and 4 months for those who did not. In patients with a favorable prognosis and symptomatic soft-tissue disease, local intervention is indicated and is associated with improved functional outcome.

Soft-tissue metastasis is a sign of systemic disease and is associated with poor prognosis regardless of primary malignancy. Several studies estimated the mean survival time after skeletal muscle metastasis to be 7.5–9 months,[26,36] which is much shorter than the median survival after diagnosis with stage-IV esophageal cancer (13 months).[37] The median survival times in our series were 8.9 months after diagnosis of soft-tissue metastasis and 24.3 months after diagnosis of primary esophageal cancer. These times are similar to those reported by earlier studies describing survival after skeletal muscle metastases from all types of cancer.[26,36] When extrapolating survival data from published case reports, we found that the median survival time after diagnosis of soft-tissue metastasis from esophageal cancer is 9 months (range 1–129 months),[4,5,12,15,16,22,24] which is similar to our findings. However, an accurate comparison cannot be made because only eight cases in the literature describe the duration of patient survival.

We found that patients with metastatic disease to soft tissue survived significantly longer (24.6 months) than patients with widespread metastases (5.2 months). Although widespread disease is a poor prognostic factor for any type of metastatic disease, it is difficult to compare survival times because only three patients in our series had metastasis to soft tissue only. Furthermore, patients with soft-tissue metastasis to subcutaneous fat without muscular involvement had significantly shorter survival time (1.3 months) compared with patients with muscular metastases (11.1 months). Only two patients had subcutaneous metastases in the absence of muscular involvement. Patients who underwent local treatment for their metastases survived significantly longer (11.1 months) than patients who did not receive local treatment (4 months), likely reflecting surgical selection bias toward patients with a favorable prognosis. Local radiation therapy was associated with significantly longer survival time (13.3 months) than no local radiation therapy (5.2 months). Of the patients who underwent local treatment, two patients (7.7%) had focal metastases to soft tissue only. In a small subset of patients with soft-tissue metastases only, aggressive local treatment may be indicated to accomplish long, disease-free survival.

We recommend local intervention in cases of oligometastatic disease to soft tissue as a curative measure, or for palliation of pain. In this subset of patients, surgery is the preferred method of local control. For patients with widespread metastatic disease, we suggest that local intervention be limited to symptomatic patients with favorable prognosis. In this subset of patients, radiation is the preferred method of local control.

Though our study assesses the largest cohort of patients with esophageal cancer and metastases to soft tissue, our sample is small (26 patients). Therefore, our survival analysis, specifically the log-rank test, may not be representative. Our study was conducted at a tertiary referral center and may not reflect the prevalence of esophageal cancer with soft-tissue metastasis in the general population. Our study also covers a 27-year period, during which prognosis and survival of patients with metastatic disease may have improved with advances in oncologic treatment. Despite these limitations, ours is the most comprehensive assessment of this rare occurrence. Further studies are needed to identify biologic factors predisposing patients with esophageal cancer to developing soft-tissue metastases.

Conclusion

Esophageal cancer has a high frequency of soft-tissue metastasis compared with other primary cancers. We estimate the prevalence of soft-tissue metastasis to be 1.9% of all patients with esophageal cancer. Adenocarcinoma is the most common histopathological type leading to soft-tissue metastasis, with most metastases occurring in the muscles of the lower extremity. Local intervention is indicated for patients in good general condition with symptomatic soft-tissue lesions or for patients with a solitary soft-tissue metastasis to accomplish long, disease-free survival. Metastases limited to soft tissue and local intervention are associated with longer survival time.

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