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CASE REPORT

Soft-tissue metastasis in esophageal cancer managed by dose escalation radiation therapy: a clinical case and review of literature

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ABSTRACT

Soft tissue metastasis in esophageal cancer is a very rare entity. A 76-year-old man was referred for a week's history of dysphagia. Upper gastrointestinal endoscopy was performed, and biopsies were consistent with an adenocarcinoma of the lower esophagus. The patient was free of metastasis on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT). The patient was treated with pre-operative chemoradiation, followed by surgery. Intravenous carboplatin [area under the curve of 2 mg/mL/min (AUC2)] and intravenous paclitaxel 50 mg/m^2 with concurrent radiotherapy (RT) (45 Gy delivered in 25 fractions of 1.8 Gy per fraction) were introduced from May 31st, 2021, to July 2nd, 2021. Lewis-Santy subtotal esophagectomy was performed, and pathology revealed a ypT3 ypN0 (0/26) L0 V1 Pn1 G3 R0. Adjuvant nivolumab was introduced for a total of 12 months. After five months of nivolumab, the patient complained of a painful left shoulder subcutaneous tumefaction in routine evaluation. Biopsy of the deltoid muscle demonstrated a poorly differentiated adenocarcinoma consistent with esophageal metastasis. Additional skeletal muscle (one) and bone metastases (two) were revealed on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT). After multidisciplinary team approach, palliative radiation therapy to all metastases, denosumab and FOLFOX were introduced. Despite initial excellent clinical outcomes, patient presented avascular necrosis of left femoral head managed by surgery but died after post-operative complications. To the best of our knowledge, it is the first reported case with rare soft-tissue metastasis occurring during adjuvant nivolumab in esophageal cancer.

Keywords: oesophageal cancer; radiotherapy; metastases

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Introduction

Soft-tissue metastases (skeletal muscle, subcutaneous fat) in esophageal cancer is a very rare entity [1, 2]. According to a 2019-report, only 27 cases of esophageal cancer with soft-tissue metastases have been described in the English-language literature [1]. Patients with soft-tissue metastases are associated with very poor prognosis, with median survival time estimated to be 7.5-9 months [1]. Soft-tissue metastases can be either limited to soft tissue only (12%) or associated with widespread dissemination (88%) [1]. In case of widespread metastases, the prognosis is even poorer (5.2 months) [1].

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There are no prospective data defining the best management of soft tissue metastases, but systemic treatment appears to be the treatment of choice [1]. However, patients with local therapies survived longer than those who did not receive local treatment (11.1 months versus 4 months) [1].

Case presentation

A 76-year-old man was referred for a week's history of dysphagia. Upper gastrointestinal endoscopy was performed, and biopsies were consistent with an adenocarcinoma of the lower esophagus (40–42 cm from the upper dental arch). Ultrasonography imaging showed a T3-T4a tumor with locoregional lymph nodes. The patient was free of metastasis on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT). After multidisciplinary tumor board discussion, weekly administration of intravenous carboplatin and intravenous paclitaxel with concurrent radiotherapy (RT) (45 Gy delivered in 25 fractions of 1.8 Gy per fraction) was decided.

Lewis-Santy subtotal esophagectomy was performed three months afterward, and pathology revealed a ypT3 ypN0 (0/26) L0 V1 Pn1 G3 adenocarcinoma with R0 margins. Postoperatively, the patient had no complications and adjuvant nivolumab at a dose of 240 mg every 2 weeks for 16 weeks, followed by a dose of 480 mg every 4 weeks (for a total of 12 months) was introduced three months afterward. At five months follow-up, the patient complained about a painful left shoulder subcutaneous tumefaction in routine evaluation. Magnetic resonance imaging (MRI) of the left shoulder showed a 26.4 × 20 mm skeletal muscle lesion, with local inflammation (Fig. 1A).

Biopsy of the deltoid muscle demonstrated a subcutaneous poorly differentiated adenocarcinoma CK7+, CDX2+, Her2 score 0, MSS phenotype consistent with known primary esophageal metastasis. Two bone metastases (a right parietal bone metastasis, and a left ischiopubic ramus metastasis with extension to the left femoral head) were revealed on ^{18}F-PET/CT (Fig. 1BC). No visceral metastases were diagnosed. Brain metastases were ruled out on MRI imaging. After initial surgical advice, there was no increased risk of fracture despite a small crack in the posterior wall.

After multidisciplinary discussion, palliative radiation therapy, followed by denosumab and FOLFOX was decided. All three metastases were treated with moderate dose escalation radiation therapy, delivering 39 Gy in 13 fractions. ^{18}F-PET/CT performed at 3 months was consistent with partial (left deltoid muscle metastasis) and complete response (right parietal bone metastasis, left ischiopubic ramus/left gluteal muscle metastases) of the irradiated lesions. Patient underwent second-line Folfox. The general condition of the patient deteriorated, and he was unfit for chemotherapy continuation. Although no in-field progression was observed, the patient died 8 months after his RT.

Discussion

Our patient presented both skeletal muscle and bone metastases without visceral metastases. In a 2014-literature review, only 5 cases of isolated skeletal muscle without visceral metastases were reported, and none had bone metastases [2]. According to a 2022-report, the four most common sites of subcutaneous soft-tissue metastases are the abdominal wall, the back, the thigh, and the chest wall [3]. The lack of sera above the abdominal esophagus makes the esophagus cancer invade adjacent structures and disseminate distantly. Our patient had an adenocarcinoma of the lower esophagus that was located on both thoracic and abdominal portions of the esophagus. Soft-tissue metastases can occur by lymphatic or hematogenous dissemination [1]. This is in accordance with the English literature, where soft tissue metastases have shown 83% of skeletal muscle metastasis secondary to primary adenocarcinoma of the lower third [1]. Associated factors predicting its risk are not well-known but local soft tissue pH, temperature and metabolite accumulation may play a role [1]. The frequent muscle movement and the resulting lactic acid production may create a difficult site for intramuscular metastases implantation [1]. However, these mechanisms remain uncertain and warrant further investigations [3]. Xi and colleagues demonstrated that pathologic response (HR, 2.417; $p < 0.001$), histologic grade (HR, 1.635; $p < 0.001$), clinical T stage (HR, 1.717; $p = 0.013$) were predictors of recurrence in patients with esophageal adenocarcinoma [4]. In our

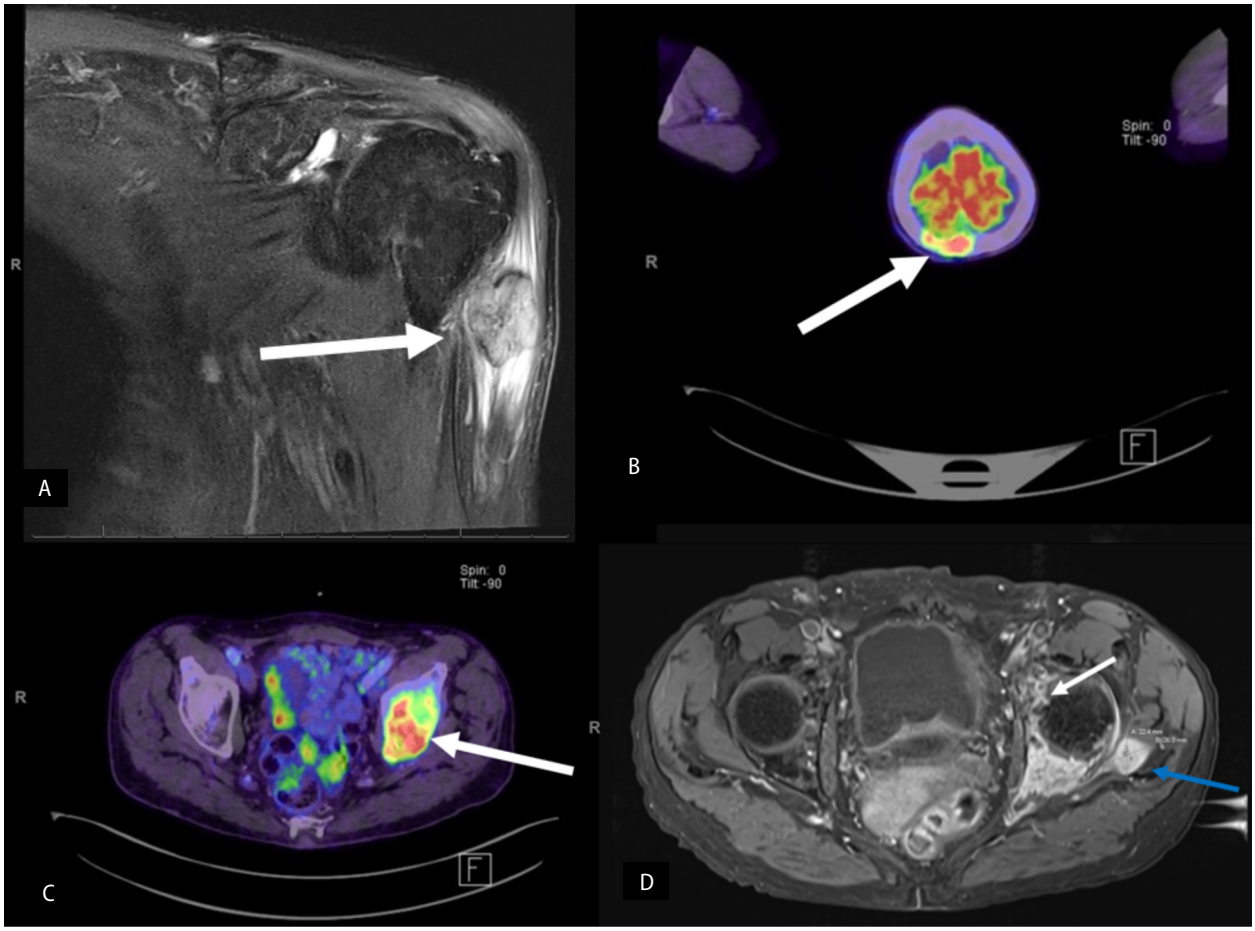

Figure 1. Soft-tissue metastases recurrence managed by dose escalation radiotherapy: metabolic and radiologic features. **A.** Magnetic resonance imaging (MRI) (May 2022), axial T1 sequences showing gadolinium uptake of left deltoid lesion (26.4 × 20 mm), with local inflammation. **B–C.** ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) image showing tracer uptake of the right parietal bone (**B**) and left iliac wing (**C**). **D.** MRI: axial T1 sequences showing gadolinium uptake of the left ischiopubic ramus metastasis with extension to the left femoral head (white arrow) and left gluteal muscle metastasis (blue arrow)

case, our patient had poorly differentiated T3-T4a esophageal adenocarcinoma of the lower third with vascular and perineural invasion within the primary tumor remaining despite trimodal therapy. Trimodal therapy did not help downstaging the disease, highlighting its aggressiveness [5]. Histologic examination of primary tumor and soft-tissue metastasis of deltoid muscle were both consistent with poorly differentiated adenocarcinoma. These clinical and pathological features may altogether have increased the risk of lymphatic and hematogenous dissemination.

As far as we know, this is the first case of subcutaneous muscle and bone metastases occurring during post-operative nivolumab in esophageal adenocarcinoma. According to a 2014-report, outfield recurrence is more likely to occur after trimodal therapy, but there is no information about the occurrence of soft-tissue metastases [6]. Pre-operative chemoradiation therapy in esophageal cancer improves locoregional control, overall survival and has an impact on both hematogenous dissemination and peritoneal carcinomatosis, but higher radiation dose >41.4 Gy may not be associated with better locoregional outcomes [6]. In phase III CheckMate 577 trial, adjuvant nivolumab following trimodal therapy was associated with improved disease-free survival (22.4 months *vs* 11.0 months, hazard ratio 0.69; 96.4% confidence interval 0.56–0.86; $p < 0.001$) [7]. Nivolumab has been shown to reduce recurrence but might not be sufficient in the management of soft-tissue or skin metastases. A 2022-case report found neither chemotherapy nor immunological checkpoint inhibitor to be effective in dif-

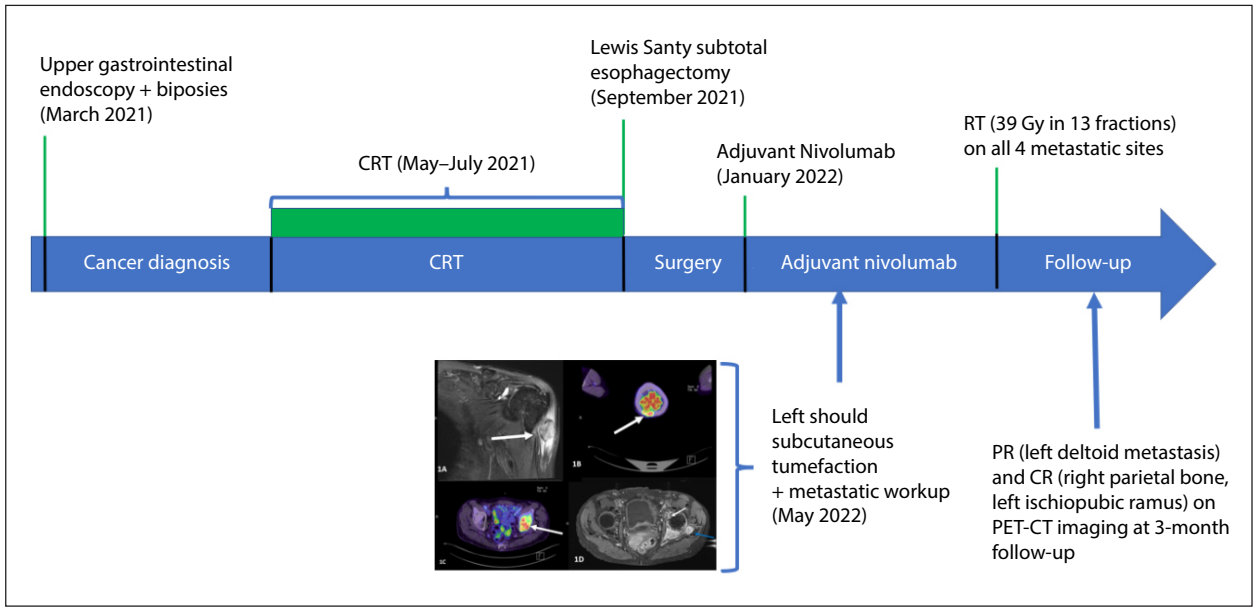

Figure 2. Soft-tissue metastases recurrence managed by dose escalation radiotherapy (RT): timeline of treatment. CRT — concurrent radiotherapy; PR — partial response; CR — complete response; PET-CT — positron emission tomography/computed tomography

fuse cutaneous metastases of esophageal squamous cell carcinoma [8]. This is in accordance with our findings. It is unclear if the delay between the end of surgery and the introduction of nivolumab (3 months) played a role. Systemic treatment alone may therefore not be enough to prevent/control soft tissue metastases. The poor clinical outcomes of soft-tissue metastases in esophageal cancer have hindered the evaluation of radiation therapy's potential role in treating such occurrences. In our patient, we delivered 39 Gy in 13 fractions, resulting in good metabolic response at 3-month follow-up. This observation is in accordance with a 2019-report, finding better survival rates in cases of local therapies compared to patients without (11.4 months *vs.* 4 months) [1]. Given the results of a 2017-report, definitive chemoradiation therapy of soft-tissue metastasis with doses as high as 70 Gy in 35 fractions had the best outcome (patient was alive without recurrence at 20 months follow-up) compared to other treatments (chemotherapy, local treatment, or both; survival range, 6–15 months) [2]. We identified in English medical literature 11 patients (excluding our case) with soft-tissue metastases in esophageal cancer managed by radiation therapy (Tab. 1) [1, 2, 9, 10]. Only one article reported total dose and fractionation underlying the lack of available data and the scarcity of this entity [2]. In cases of isolated soft-tissue metastases in oligometastases or oligoprogression, dose escalation using stereotactic body radiation therapy could be a good approach to consider for achieving local control and improved overall survival. This strategy would offer several advantages, such as ablative treatment, short treatment time, non-invasive procedure, and better recovery [11].

Melanoma, or lung, kidney or breast adenocarcinoma are usually the primaries of secondary soft tissue tumor locations [12]. The esophageal carcinoma is more rarely associated with soft tissue metastases and their occurrence, under immune checkpoint blockade, raises question of a potential specific immunosuppressive condition of this anatomical site.

The brain is known as a sanctuary site for tumor cell, protected from drugs by the meningeal blood-brain barrier. In case of immunotherapy treatment, the sanctuary for tumor cells may be the place where the unfavorable microenvironment allows the tumor growth despite the PD-L1 blockade.

Some organs have been described as containing a particular microenvironment favoring metastases occurrence, especially the lung [13]. However, there are no specific data for the soft tissue metastases in this field.

Table 1. Cases of subcutaneous metastases in esophageal cancer treated with radiotherapy: review of literature

Article	Number of cases	Symptoms	Treatment	RT dose/fractionation	Follow-up	Outcome
Present case	1	80-year-old woman **Location:** left deltoid muscle **Other sites:** Right parietal bone metastasis, Left ischiopubic ramus metastasis/left gluteal muscle metastases **Histology:** adenocarcinoma **Time to diagnosis:** 12 months **Imaging:** MRI of left deltoid muscle	RT	39 Gy in 13 fractions BED α/β 10 = 50.7 Gy	3 months 8 months	Partial response and complete response on PET-CT imaging Death
El Abiad [1]	8	No specific information given	4 cases with radiation only 4 cases with radiation and surgical resection	Not reported	13.3 months	Not reported
Fujimoto [2]	1	77-year-old man **Location:** Left forearm (solitary) **Histology:** SCC **Time to diagnosis:** 14 months after esophagectomy **Imaging:** MRI of the left upper extremity	Chemoradiotherapy (2 cycles of 5-fluorouracil 700 mg/m^2 on days 1 to 5, combined with cisplatin 70 mg/m^2 on day 1)	70 Gy in 35 fractions BED α/β 10 = 70 Gy	20 months	No recurrence
Smyth [9]	1	50-year-old man **Location:** left buttock **Histology:** SCC (de novo metastatic cancer) **Imaging:** CT-scan	2-weeks palliative RT	10 fractions Total dose not reported	Not reported	Not reported
Puri [10]	1	69-year-old man **Location:** posterior neck, left abdomen, right pelvis **Histology:** SCC **Time to diagnosis:** 2.5 years after initial diagnosis	Chemotherapy + RT	Not reported	8 months	Death

BED — biological effective dose ; RT — radiation therapy; SCC — squamous cell carcinoma; PET — positron emission tomography; CT — computed tomography; MRI — magnetic resonance imaging

It would have been extremely interesting to perform a deep molecular analysis of the soft tissue metastasis but also to describe the tumor microenvironment biomarkers, as tumor infiltrating lymphocytes (TILs), cancer associated fibroblasts (CAFs) and myeloid-derived suppressor cells (MDSCs) [14].

Unfortunately, our patient couldn't benefit from the second line systemic oncologic treatment and there was no time for any extensive molecular analysis. We hope this case report will encourage biological understanding of unusual tumor localizations, especially for patients treated by immunotherapy.

Conflict of interest

Authors declare no conflict of interests.

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