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Mediastinum & Esophagus: Short Report

Secondary Esophageal Cancer After Hematopoietic Stem Cell Transplant: An Institutional Case Series

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ABSTRACT

BACKGROUND Development of secondary esophageal cancer after hematopoietic stem cell transplantation has been described; however, there is little consensus on treatment and surveillance for these patients. The objective of this study was to describe our experience treating patients with secondary esophageal cancer.

METHODS A retrospective chart review of prospectively collected data was performed to identify patients who underwent hematopoietic stem cell transplantation from 1997 to 2012 and in whom esophageal cancer developed later.

RESULTS A total of 5066 patients underwent hematopoietic stem cell transplantation, and esophageal cancer developed in 11 (0.2%) of these patients. The median time to diagnosis of esophageal cancer after hematopoietic stem cell transplantation was 11 years (interquartile range, 8.5 to 14 years). Four patients received a diagnosis of stage III or IV disease. Seven patients underwent esophagectomy, 6 patients after neoadjuvant treatment. Three patients experienced adverse events postoperatively, all grades II and IIIa. Two surgical patients died of distant recurrence 2 years and 3 years, respectively, after their esophageal cancer diagnosis. The other 5 surgical patients have not experienced recurrence of their esophageal cancer.

CONCLUSIONS For patients with secondary esophageal cancer, esophagectomy after neoadjuvant treatment has acceptable morbidity and may be a viable option for this cohort.

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Hematopoietic stem cell transplantation (HSCT) is a standard treatment for patients with hematologic diseases.[1] Advances in transplantation have increased the number of long-term survivors.[2] Consequently, the incidence of late effects of the procedure has also increased, which include secondary malignant neoplasms and chronic graft-vs-host disease (cGVHD).[3] These secondary cancers can account for up to 10% of deaths in patients who survive 2 years or more after HSCT, and the incidence increases with time from transplantation.[4]

IN SHORT

- Treatment guidelines and surveillance recommendations for patients with secondary esophageal cancer after stem cell transplant are unclear.
- For patients with secondary esophageal cancer, esophagectomy after neoadjuvant treatment may be a viable option.
- Surveillance may be warranted as early as 1 year after stem cell transplantation or sooner if symptoms develop.

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Abbreviations and Acronyms

allo-HSCT = allogenic hematopoietic stem cell transplantation
auto-HSCT = autologous hematopoietic stem cell transplantation
cGVHD = chronic graft-vs-host disease
DFCI = Dana-Farber Cancer Institute
EC = esophageal cancer
HSCT = hematopoietic stem cell transplantation
IQR = interquartile range
NAC = neoadjuvant chemotherapy
nCRT = neoadjuvant chemoradiation
SCC = squamous cell carcinoma

Main risk factors for esophageal cancer (EC) include alcohol intake, obesity, and gastroesophageal reflux disease.[5] The publication of the ChemoRadiotherapy for Oesophageal Cancer followed by Surgery Study (CROSS) in 2013 revolutionized the management of patients with EC and demonstrated an impressive survival benefit with neoadjuvant chemoradiation (nCRT).[6] Several studies have demonstrated almost a 10-fold greater risk in development of secondary EC after allogenic HSCT (allo-HSCT).[7] Unlike for patients with primary EC, there is little consensus on treatment and surveillance for patients with secondary EC.

Given the uncertainty in management of these patients, we examined our experience treating individuals with secondary EC after HSCT. We hypothesized that patients who underwent neoadjuvant therapy and esophagectomy will have acceptable morbidity and mortality and can undergo the traditional treatment typically administered for EC.

PATIENTS AND METHODS

Institutional Review Board approval was obtained at Dana-Farber Cancer Institute (DFCI; Boston, MA; #21-576) and Brigham and Women's Hospital (Boston, MA; #2014P002478). Patients with EC were identified through a query of the DFCI's bone marrow transplant repository. This repository includes all patients who have undergone autologous HSCT (auto-HSCT) and allo-HSCT since 1997. The database captures basic disease and transplant demographics and relevant transplant outcomes, including secondary malignancies. We additionally conducted a query of the divisional outcomes database within the Division of Thoracic Surgery at Brigham and Women's Hospital for patients who had undergone esophagectomy for secondary EC at another institution besides DFCI. This prospective database monitors perioperative variables and outcomes for all surgical patients and is audited twice weekly by attending surgeons. Esophagectomies were classified as open, minimally invasive (thoracoscopic or robotic surgery), or hybrid (combination of open and either of the 2 minimally invasive approaches).

RESULTS

HEMATOLOGIC MALIGNANCY. From 1997 to 2012, 5066 patients underwent HSCT at DFCI, and secondary EC developed in 11 of these patients. Seven patients (64%) were female. Four patients (36%) underwent auto-HSCT, 5 patients underwent allo-HSCT (45%), and 2 patients (18%) underwent allo-HSCT after failed auto-HSCT. Median age at transplantation was 42 years (interquartile range [IQR], 36-57 years). After transplantation, 5 patients (45%) experienced cGVHD. Three of these patients are still receiving long-term immunosuppressive therapy (Table 1).

SECONDARY ESOPHAGEAL CANCER: PATIENT AND TUMOR CHARACTERISTICS. The median age of diagnosis was 58 years (IQR, 48-62 years). The median time to diagnosis of EC was 11 years after HSCT (IQR, 8.5-14 years). Seven patients had squamous cell carcinoma (SCC), 3 had adenocarcinoma, and 1 had poorly differentiated carcinoma. Seven patients received a diagnosis of early-stage cancer (clinical stage I or II; 64%). Four ECs were at the distal esophagus or gastroesophageal junction, 3 were at the midesophagus, and 4 were at the upper esophagus (Table 2). The median follow-up for the entire cohort was 13 years (IQR, 2-23 years). Four patients did not undergo esophagectomy, and all are deceased. Additional details for these patients are included in the Supplemental Table.

SECONDARY ESOPHAGEAL CANCER: SURGICAL PATIENTS. Of the 7 patients who underwent esophagectomy, 5 received nCRT. Case 3 received only neoadjuvant chemotherapy (NAC) given a history of mantle and axillary radiation for HSCT. Case 11 did not receive nCRT for EC given a history of mantle radiation for Hodgkin lymphoma and recent administration of chemotherapy for cecal cancer. Four patients experienced side effects of nCRT. Treatment was stopped early for 2 patients as a result of failure to thrive and thrombocytopenia. The other 2 patients experienced dehydration and lightheadedness but were able to complete their treatment course.

There were 2 open esophagectomies, 4 minimally invasive, and 1 hybrid procedure. Five patients underwent a McKeown esophagectomy, and 1 patient had an Ivor Lewis esophagectomy. One patient (case 5) underwent a partial cervical esophagectomy and pharyngectomy for SCC involving the inferior pharynx and the left and posterior aspect of the cervical esophagus. A

TABLE 1 Hematologic Malignancies of the Cohort

Case	Age at Transplantation, y/Sex	Hematologic Disorder	Recurrence of Hematologic disorder	Type of HSCT	HSCT Conditioning Regimen	Chronic Graft vs Host Disease?	Immunosuppression
1	35/female	Myelodysplastic syndrome	No	Allogeneic	Total body irradiation, cyclophosphamide	Yes – vulva and vagina	Stopped 13 years after HSCT
2	61/male	Multiple myeloma	No	Autologous	Melphalan	N/A	No
3	41/female	Hodgkin lymphoma	Yes	Autologous followed by allogeneic	Cytarabine, etoposide, carmustine	No	Stopped 1 year after HSCT
4	56/male	Multiple myeloma	No	Autologous	Melphalan	N/A	No
5	24/female	Fanconi anemia	No	Allogeneic	Fludarabine, busulfan, cyclophosphamide	No	Stopped 3 years after HSCT
6	30/female	Hodgkin lymphoma	Yes	Autologous followed by allogeneic	Cytarabine, etoposide, carmustine	Yes – oral, cutaneous	Currently taking
7	59/female	ALL	No	Allogeneic	Fludarabine, busulfan	Yes – ocular, autoimmune hepatitis	Currently taking
8	42/male	Non-Hodgkin lymphoma	Yes	Allogeneic	Cyclophosphamide, total body irradiation	Yes – cutaneous	Stopped 15 years after HSCT
9	61/male	AML	Yes	Allogeneic	Fludarabine, busulfan	Yes – cutaneous, pulmonary	Was still taking at time of death
10	38/female	Non-Hodgkin lymphoma	Yes	Autologous	Cytarabine, etoposide, carmustine	N/A	No
11	46/female	Hodgkin lymphoma	Yes	Autologous	Cytarabine, etoposide, carmustine	N/A	No

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; N/A, not applicable.

right radial forearm free flap was used for reconstruction (Table 3).

Three patients experienced adverse events postoperatively, all grades II and IIIa (Table 3). There were no 30-day or 90-day mortalities. Two patients had distant recurrence of EC and died 2 years and 3 years after the EC diagnosis, respectively. The other 5 patients who are still alive were seen in clinic within the last year, and

TABLE 2 Details of the Secondary Esophageal Malignancies of the Cohort

Case	Time Between HSCT and EC Diagnosis, y	Histologic Subtype of EC	Location of EC	Clinical Staging of EC	Initial Treatment	Recurrence of EC	Survival (Time From EC Diagnosis to Death or Recent Follow-up)
1	13	Squamous cell carcinoma	Middle	II	Neoadjuvant chemoradiation, esophagectomy	No	Alive (13 y)
2	5	Adenocarcinoma	Distal	I	Neoadjuvant chemoradiation, photodynamic therapy	Yes – esophagus	Dead – relapsed multiple myeloma (5 y)
3	8	Squamous cell carcinoma	Middle	I	Neoadjuvant chemotherapy, esophagectomy	Yes – posterior mediastinum, pleura	Dead – advanced disease (2 y)
4	1	Adenocarcinoma	Distal	IV	Chemotherapy	No	Dead – advanced disease (1 y)
5	10	Squamous cell carcinoma	Upper	III	Neoadjuvant chemoradiation, esophagectomy	Yes – lung, liver	Dead – advanced disease (3 y)
6	15	Squamous cell carcinoma	Middle	II	Neoadjuvant chemoradiation, esophagectomy	No	Alive (6 y)
7	9	Squamous cell carcinoma	Upper	III	Neoadjuvant chemoradiation, esophagectomy	No	Alive (2 y)
8	19	Poorly differentiated carcinoma	Distal	IV	Chemoradiation, pembrolizumab	No	Dead – cardiac arrest (2 y)
9	13	Adenocarcinoma	Distal	II	Chemoradiation	No	Dead – unknown (11 mo)
10	21	Squamous cell carcinoma	Upper	II	Neoadjuvant chemoradiation, esophagectomy	No	Alive (3 y)
11	11	Squamous cell carcinoma	Upper	II	Esophagectomy	No	Alive (2 y)

EC, esophageal cancer; HSCT, hematopoietic stem cell transplantation.

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TABLE 3 Additional Details of the Esophagectomy Cohort

Case	Type of Neoadjuvant Treatment	Type of Esophagectomy	Pathologic Staging of EC	Adverse Events	Adjuvant Treatment
1	Carboplatin/paclitaxel, radiation	Open, McKeown	I	None	None
3	Cisplatin/5-fluorouracil	Minimally invasive Ivor Lewis	II	Grade II – hypotension requiring 5% albumin	None
5	Carboplatin/paclitaxel, radiation	Partial cervical esophagectomy/pharyngectomy	IVb	None	Nivolumab and cetuximab; chemoradiation (carboplatin/ paclitaxel)
6	Carboplatin/paclitaxel, radiation	Minimally invasive McKeown	I	Grade II – hypotension requiring pRBC transfusion	None
7	Carboplatin/paclitaxel, radiation	Minimally invasive McKeown	II	Grade II – laryngeal nerve paralysis requiring vocal cord injection; atrial fibrillation requiring metoprolol	None
10	Carboplatin/paclitaxel, radiation	Hybrid McKeown	II	None	Nivolumab
11	None	Robotic McKeown	IA	None	None

EC, esophageal cancer; pRBC, packed red blood cells.

none have had a recurrence of EC (Table 2). Two of those five patients continue receiving immunosuppressive therapy for cGVHD.

COMMENT

This case series describes the development of secondary EC in adults after allo-HSCT and auto-HSCT. In our cohort, 11 patients had secondary EC, 5 patients after allo-HSCT and 4 after auto-HSCT. Two patients underwent allo-HSCT after failed auto-HSCT. Seven patients underwent esophagectomy, and 6 of these patients had received neoadjuvant therapy. Five patients (all surgical) are still alive, and 2 are actively receiving an immunosuppressive regimen for cGVHD. Additionally, this cohort includes patients with both adenocarcinoma and SCC of the esophagus, and there had been no previously documented cases of esophageal adenocarcinoma after HSCT.

HSCT-treated patients have a higher risk of secondary EC development compared with the general population.[7] cGVHD (which can develop after allo-HSCT) is a significant risk factor for secondary EC and has been reported previously only for esophageal SCC.[8] Interestingly, of the 5 patients in our cohort who had cGVHD, 3 had SCC, 1 patient had adenocarcinoma, and the other patient had poorly differentiated carcinoma. The patient with adenocarcinoma also had a history of Barrett esophagus, a well-known risk factor for this cancer subtype.[5] The patient with poorly differentiated carcinoma did not have a remarkable medical history besides glaucoma and hypothyroidism. Prolonged immunosuppressive therapy for >24 months is also a risk factor for secondary EC.[8] Seven patients in our cohort were receiving an immunosuppressive regimen after HSCT, and 2 had stopped their regimen several years before their secondary EC diagnosis.

The previously reported median time to diagnosis of EC after HSCT is approximately 7 to 9 years.[8] The median time to diagnosis in our cohort was 11 years, with the earliest diagnosis occurring 1 year after transplantation. To our knowledge, there were no obvious predisposing risk factors leading to such an early development of EC. The patient was 56 years old at the time of HSCT, did not have a unique hematologic malignancy, and had not received an uncommon chemotherapy regimen. Given the short time interval from transplantation to cancer diagnosis, other unknown predisposing risk factors could have been present; therefore, the EC cannot solely be attributed to the HSCT.

Treatment guidelines for these patients are unclear, and studies differ on the benefits of NAC, definitive radiotherapy, or nCRT. In our cohort, 7patients underwent esophagectomy. Five patients received nCRT, 1 patient received NAC, and 1 patient underwent upfront esophagectomy. Only 3 patients experienced adverse events postoperatively, all grades II and IIIa. Our sample is not large enough to detect significant differences in postoperative adverse events among patients who received nCRT vs NAC or upfront surgery. However, we believe the adverse events that developed after nCRT were acceptable, and patients fully recovered without experiencing any long-term effects. There were no 30-day or 90-day mortalities. Five of the 7 surgically treated patients are currently alive. Two are deceased

from distant disease recurrence. Although our cohort is small, these observations suggest that neoadjuvant therapy followed by esophagectomy may be an appropriate treatment option for these patients.

Surveillance recommendations for secondary solid tumors after HSCT are also unclear. Studies have acknowledged the need for prolonged, lifelong surveillance, but specific recommendations are lacking.[8] Considering that 2 of the patients in our cohort had EC much earlier than the reported median of 7 to 9 years (at 1 year and 5 years after HSCT, respectively), surveillance may be warranted as early as 1 year after transplantation or sooner than 1 year if symptoms develop.

This series adds valuable data to existing knowledge on secondary malignant neoplasms after HSCT. Some of our findings align with those of previous literature. However, important differences are also seen that underscore the need for continued investigation.

The Supplemental Table can be viewed in the online version of this article [https://doi.org/10.1016/j.atssr.2024.02.014] on http://www.annalsthoracicsurgery.org.

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