Patient demographics, clinical characteristics, treatment patterns, and survival outcomes associated with first-line treated unresectable advanced, metastatic, and recurrent esophageal squamous cell carcinoma in the US

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Introduction

- Globally, 90% of esophageal carcinoma (EC) cases have squamous cell histology (ESCC). A recent study found the 1-year and 5-year cause-specific survival of patients with ESCC in the US SEER-Medicare database was 43.8% and 18.9% respectively, with a median survival of 10 months[1]
- Current first line (1L) treatment guidelines for unresectable advanced, recurrent, or metastatic (adv/met) ESCC recommend combining platinum-based chemotherapy (eg, carboplatin, oxaliplatin, cisplatin) and fluoropyrimidines (eg, 5FU, capecitabine), of with taxanes (eg, paclitaxel, docetaxel), or with irinotecan[2]

Objectives

- The goal of this real-world study was to better understand patient characteristics and median overall survival (mOS) of US patients the Flatiron database with unresectable advanced, recurrent, or metastatic ESCC, who received 1L chemotherapy or best supportive care (BSC)

Methods

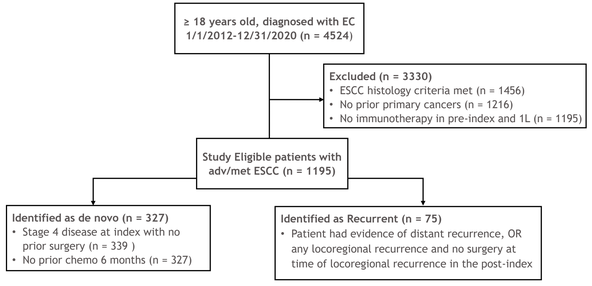
- This was a real-world, observational retrospective analysis of US patients identified in the Flatiron oncology electronic medical record (EMR) database, representing 280 ambulatory oncology clinics at 800 sites
- EMR were examined from an 8-year period, 01/01/2012 through 12/12/2020
- The initial EC diagnosis date was the date of the earliest EC record
- The index date was the date of adv/met ESCC diagnosis, defined as the earliest date when locally-advanced ESCC was determined to be unresectable or when metastases were identified
- Included patients, on the initial EC diagnosis date, were aged ≥ 18 years, had ≥ 1 outpatient medical record with primary ICD-10 diagnostic code for EC (ICD-9 code: 150.X; ICD-10 code: C15.X), and had ESCC histology
- Excluded patients had a diagnosis for another primary cancer on or before the initial EC diagnosis date; or received checkpoint inhibitor immunotherapy and/or other immunotherapy agents for other immune-related conditions in the pre-index or first-line treatment in the post-index
- Patients with de novo adv/met ESCC were those whose initial EC diagnosis date was the same as the date of adv/met ESCC diagnosis, excluding those who had surgical resection before enrolment or had chemotherapy within 6 months before enrolment
- Patients with recurrent adv/met ESCC were those found to have locoregional or distant metastatic disease following complete surgical resection and no surgery at time of locoregional recurrence in the post-index
- Patient demographics, clinical characteristics, and treatment patterns were presented by descriptive statistics over the index and post-index periods. Descriptive statistics of continuous variables were generated as means, medians, and standard deviations, whereas categorical variables were presented as raw frequencies or percentages
- Kaplan-Meier survival curves were used to estimate mOS for patients receiving 1L chemotherapy or BSC for the overall population, for select demographic and clinical sub-groups, and for patients with who the initiation of each line of therapy and reported

Results

Patient selection

- Of 1456 patients identified with EC, 402(27.6%) met inclusion and exclusion criteria and were identified as patients with adv/met ESCC, of which 327 (22.5%) had de novo and 75 (5.2%) recurrent disease **(Figure 1)**

Figure 1. Patient selection consort diagram



Demographics and clinical characteristics

- A thorough initial exploration of demographic and clinical variables revealed that potentially important variables such as Eastern Cooperative Oncology Group (ECOG) performance status, comorbid disease, laboratory parameters (including PD-L1 status), and vital statistics were not uniformly captured over the observation windows of this study. Only sex, age, index year, and stage at identification were consistently captured and are reported
- In the treated and BSC cohorts, the majority of patients were male (70.6%, 64.6%, respectively), white (56.7%, 52.2%, respectively), and about 80% had Stage 4 disease **(Table 1)**
- For 61.7% of treated patients and 48.8% of patients receiving BSC, the index date occurred within the last 4 years of the study (i.e., during or later than 2016) **(Table 1)**

Treatment patterns

- Of the 289 patients with recurrent or de novo ESCC receiving 1L treatment, 117 (40.5%) received carboplatin and paclitaxel combination and 67 (23.2%) received FOLFOX (fluorouracil, leucovorin and oxaliplatin combination) **(Table 2)**

Table 1. Demographics and clinical characteristics: all patients

Variable	1L Treatment n = 289	BSC n = 113	All patients n = 402
Sex			
Male, n (%)	204 (70.6)	73 (64.6)	277 (68.9)
Mean age, years (SD)	66.0 (9.2)	67.3 (9.7)	
Race, n (%)			
Asian	17 (5.9)	4 (3.5)	21 (5.2)
Black	47 (16.3)	20 (17.7)	67 (16.7)
Other race	25 (8.7)	17 (15.0)	42 (10.4)
White	164 (56.7)	59 (52.2)	223 (55.5)
Missing	36 (12.5)	13 (11.5)	49 (12.2)
Advanced diagnosis year, n (%)			
< 2016	111 (38.3)	58 (51.2)	169 (42.0)
≥ 2016	178 (61.7)	55 (48.8)	233 (58.0)
Stage at identification, n (%)			
Stage I-III	44 (15.1)	16 (14.3)	60 (14.9)
Stage IV	240 (83.0)	88 (77.9)	328 (81.6)
Unknown/undocumented	5 (1.9)	9 (7.8)	14 (3.5)

- Of these, 124 (42.9%) proceeded to 2L. Of those in 2L, 28 (22.6%) received FOLFOX and 20 (16.1%) received carboplatin and paclitaxel **(Table 2)**
- After receiving 2L therapy, 54 (43.5%) patients went on to 3L. The most common 3L regimen was pembrolizumab monotherapy (12.9%, n = 7), followed by FOLFIRI (fluorouracil, leucovorin, and irinotecan combination) (11.1%, n = 6) **(Table 2)**

Table 2. Treatment patterns for all treated patients

Treatment characteristics	Treatment regimen	n	%
Treatment regimens (top 3)			
1st line (n = 289)		289	
Regimen 1 (n, % of 1st line)	Carboplatin + paclitaxel	117	40.5%
Regimen 2 (n, % of 1st line)	FOLFOX	67	23.2%
Regimen 3 (% of 1st line)	Cisplatin + 5FU	15	5.2%
Proportion treated of preceding line population (%)			-
Proportion treated of base population (%) (n = 402)			71.9%
2nd line (N)		124	
Regimen 1 (% of 2nd line)	FOLFOX	28	22.6%
Regimen 2 (% of 2nd line)	Carboplatin + paclitaxel	20	16.1%
Regimen 3 (% of 2nd line)	Nivolumab monotherapy	17	13.7%
Proportion treated of preceding line population (%)			42.9%
Proportion treated of base population (%) (n = 402)			30.8%
3rd line (N)		54	
Regimen 1 (% of 3rd line)	Pembrolizumab monotherapy	7	12.9%
Regimen 2 (% of 3rd line)	FOLFIRI	6	11.1%
Regimen 3 (% of 3rd line)	Irinotecan monotherapy, capecitabine monotherapy	5	9.3%
Proportion treated of preceding line population (%)			43.5%
Proportion treated of base population (%) (n = 402)			13.4%

Overall survival

- The mOS of all treated patients was 10.2 months (8.7–12.3)
- The mOS of patients receiving BSC was 3-fold shorter at 3.4 months (2.5-4.4)
  - The 91 (80.5%) patients receiving BSC who died in the post-index period had a mOS of 2.7 months (2.3–3.5) observation

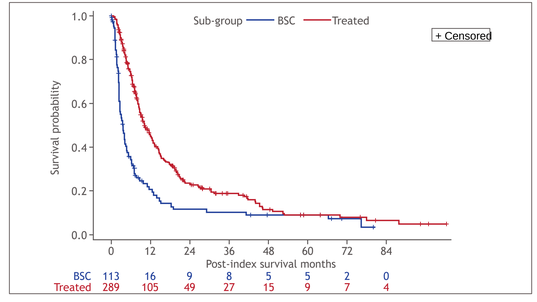
Treatment-related survival by line of treatment

- The mOS from start of 1L therapy was 8.2 months (7.0–10.2; n = 289)
  - The mOS was 7.0 months (6.0–8.0) for 165 (57.1%) patients who did not proceed to 2L, of whom only 38 (23.0%) survived the post-index observation period **(Table 3)**
- The mOS from start of 2L therapy was 6.8 months (5.5–9.8; n = 124)
  - Of 124 patients who received 2L therapy, 70 (56.5%) did not proceed to 3L and had a median survival of 12.5 months (9.4–14.9). Of these, only 21 (30.0%) survived the post-index observation period **(Table 3)**
- The mOS from start of 3L therapy was 5.9 months (4.8–10.7; n = 54)
- **Figure 2** displays the Kaplan-Meier curve for patients in the treated and BSC cohorts

Table 3. Median survival from date of adv/met ESCC diagnosis, months (range)

	n	
Total population, N = 402	402	8.2 (7.2, 9.5)
BSC only, n = 113	113	3.4 (2.5, 4.4)
Died	91	2.7 (2.3, 3.5)
Survived	22	Unmeasurable
Received first line	289	10.2 (8.7, 12.3)
Did not receive 2nd line	165	7.0 (6.0, 8.0)
Did not receive 2nd line and died	127	5.9 (4.6, 6.7)
Survived with no further line	38	Unmeasurable
Received second line	124	16.0 (14.3, 20.8)
Did not receive 3rdt line	70	12.5 (9.4, 14.9)
Did not receive 3rd line and died	49	9.5 (7.8, 12.2)
Survived and no further line	21	Unmeasurable
Received third line	54	21.1 (16.0, 30.5)

Figure 2. Kaplan-Meier curve (treated vs. BSC)



Survival Sub-Group Analyses

- The mOS for treated and BSC patients < 65 years old and those ≥ 65 years old is similar
- Women appear to have longer median survival times when compared to males (12.5 vs 9.6) among treated patients
- Patients with recurrent ESCC appear to have a much longer mOS when compared to Stage 4, 4A and 4B de novo patients in both the treated and BSC patient populations

Limitations

- Misclassification bias due to errors in coding was possible with this EMR-based database
- It is possible that not all patient-level data may have been captured for these patients across the observation period of this study, especially the care patients receive at non-Flatiron facilities
- Flatiron is a curated database where patient status as advanced ESCC as well as decision rules for lines of treatment were based on criteria or business rules established by Flatiron and may not reflect general clinical practice in the US.
- Key variables that may impact survival outcomes such as ECOG status, comorbid disease, laboratory parameters, etc., were not well populated across the study eligible population
- Patients who received care from Flatiron-affiliated centers may not represent patients treated elsewhere and thus, may not be generalizable to the ESCC US population

Conclusions

- Treated patients with de novo or recurrent adv/met have a mOS of 10.2 months (8.7—12.3) 3-fold longer than patients receiving BSC: 3.4 months (2.5—4.4)
- In this study, 57.1% of 1 L treated patients did not go on to receive 2L
- Outcomes for patients treated with 1L chemotherapy for ESCC are poor, and there remains a large unmet need in this population. In addition, BSC patients who may not have been able to tolerate standard chemotherapy agents or who were poor candidates for resective surgery may also obtain a survival benefit from early treatment with novel treatment options

References

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