Treatment Patterns Among Metastatic Esophageal Cancer Patients in the US: A Retrospective Analysis of Health Insurance Claims Data

Jacob Silvers

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Committee:

Josh Carlson

Ryan Hansen

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University of Washington

Abstract

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Jacob Silvers

Chair of the Supervisory Committee:

Josh Carlson

Department of Pharmacy

Background: Esophageal cancer is a common cancer with over 19,000 new cases in the United States estimated for the year 2021. The National Comprehensive Cancer Network guidelines recommend ablation or surgery for patients that have early stages of the cancer. For unresectable or metastatic esophageal cancer, a variety of systemic treatments are recommended, including chemotherapies, monoclonal antibodies, and targeted therapies. Several recent treatment pattern studies have been published but none are specific to esophageal cancer and without restrictive exclusion criteria.

Objective: Characterize treatment patterns among patients diagnosed with metastatic esophageal cancer during the years 2017, 2018, and 2019. Analyze time to change in treatment for the first line of therapy and probability of treatment initiation by year.

Methods: The source data was compiled from the IBM MarketScan Commercial databases. Patients were included in the analysis if they had at least 2 outpatient diagnoses or 1 inpatient diagnosis for metastatic esophageal cancer. Patients were required to have continuous enrollment for 6 months prior to the index date and for 1 month after the index date. The index date was the second outpatient diagnosis or the first inpatient diagnosis of esophageal cancer. Analysis of treatment patterns and lines of therapy was performed by combining claims for cancer treatments for each patient within a specified timeframe and determining if the treatment was contained in the NCCN guidelines. Kaplan-Meier survival methods were used to determine treatment persistence, and a logistic regression was used to analyze the odds of treatment initiation by year.

Results: In total, 190 patients were identified who matched eligibility criteria. The treatment pattern analysis resulted in 52 different treatment combinations being identified across 4 lines of therapy, and 120 patients received at least a one line of therapy. The most common treatments were a combination of fluorouracil and oxaliplatin and a combination of paclitaxel and carboplatin. First line treatment persistence based on the Kaplan-Meier analysis showed that the median duration of treatment for patients who received 2 or more lines of therapy was 106 days, and the median for patients who received only one line therapy was 49 days. The results of the

logistic regression for treatment initiation by year showed no significant association between year of initiation and odds of starting treatment.

Conclusion: The results of the treatment pattern analysis clearly show that a combination of fluorouracil and oxaliplatin is the most common first line treatment in metastatic esophageal cancer. The treatment persistence curve demonstrated a considerably longer duration of median first line therapy for patients who received additional lines of therapy beyond the first. The mean for all patients based on first line of therapy duration was greater than the median suggesting a left skew with a few patients having long first line of therapy times. Despite changes in esophageal cancer guidelines and the inclusion of new therapies over time, the logistic regression showed no significant findings; indicating that recommendations and availability of medications had limited effect on the odds of treatment initiation.

Contents

Background

In 2021 there will be an estimated 19,260 new cases of esophageal cancer in the United States, and by the age of 79, 3.7% of men will develop gastric related cancer[2,4]. Squamous cell carcinoma (SCC) is the most common histology for esophageal cancer and accounts for approximately 87% of cases; however, recently in Western countries adenocarcinoma has become the most prevalent histology[10]. According to 2017 SEER statistics the rate of adenocarcinoma in the United States was 2.6 per 100,000 persons and the rate of SCC was 1.2 per 100,000 persons[2]. The incidence rate of adenocarcinoma in the United States increased over 7 times from 1973 to 2012[10].

The two types of esophageal cancer differ in location and risk factors. Squamous cell carcinoma typically occurs in younger patients (early 50s) that are frequent consumers of alcohol and nicotine while adenocarcinoma often occurs in older patients (early 60s) who have a high BMI and suffer from GERD. Squamous cell carcinoma tends to be located higher in the esophagus above the tracheal bifurcation while adenocarcinoma is almost always found lower in the esophagus and preceded by a condition known as Barrett's Esophagus[9]. In Barrett's esophagus the lower part of the esophageal mucosa is replaced with intestinal epithelium. The relative risk for developing esophageal cancer with this condition is 10 times greater than the general population, and Barrett's esophagus occurs in approximately 15% of those with GERD[9]. The prognosis for SCC is worse than adenocarcinoma (ACC) for local and regional diagnosis but is slightly better at distant/metastatic diagnosis. In the United States the 5-year survival for localized SCC is only 31.9% however, the localized survival rate for ACC is 52.9%[2].

This study is focused on patients who have metastatic esophageal cancer and who are treated with systemic therapy. The NCCN guidelines differ slightly by histology on when systemic therapy is recommended, but as a summary, any patient with a tumor that has invasion of nearby tissue may be a candidate for chemotherapy regardless of histology[3]. Systemic therapy for these cancers as treatment for metastatic or locally advanced disease involves multiple aggressive chemotherapies, and patients will often undergo several lines of therapy. The NCCN guidelines prefer a combination a carboplatin, fluoropyrimidine, and pembrolizumab or trastuzumab with chemotherapy as first line systemic treatments. The strength of the recommendations for most treatment combinations is based upon lower-level evidence but with uniform consensus with a recommendation category of 2A. For HER2 overexpression in adenocarcinoma trastuzumab or a bioequivalent is added to fluorouracil and oxaliplatin. In HER2 negative esophageal cancers immunotherapies like pembrolizumab and nivolumab may be indicated. Other targeted treatments, such as ramucirumab, entrectinib, and larotrectinib are recommended in special cases or if other regimens are not appropriate[3].

Scientific Rationale

Although several studies have been published on the treatment patterns of esophageal cancer patients, they are now somewhat outdated and limited by their eligibility criteria that restricted patients based on treatments. One study explicitly excluded targeted and immunotherapies. This exclusion criteria would result in the removal of treatments that are currently considered first line therapy, such as

pembrolizumab and nivolumab. NCCN guidelines currently recommend immunotherapy at every line of therapy and the popularity of treatment with immunotherapy is likely to increase. Therefore, the present study examined the treatment patterns in metastatic esophageal cancer, including patients treated with immunotherapy and targeted therapy in the United States. In addition, the present study included investigation into potential confounding based on the year of treatment initiation. The characterization of esophageal cancer treatment patterns with the most recently available data is paramount to developing new systemic and immunotherapies.

Objective

The objective of this observational study was to characterize treatment patterns in metastatic esophageal cancer patients by line of therapy and by prevalence of treatments over time. Secondary objectives were 1) to estimate the time to end of first line treatment using a time to event analysis and 2) to assess the differences in first line treatment initiation over time.

Methods

Data Source

The source data was compiled from the IBM MarketScan® Commercial databases. The IBM MarketScan Commercial databases are built by collecting data from employers and health plans. The data is based on a large convenience sample which represents primarily large employers and private health plans. MarketScan data includes eligibility, claims, encounters, plan information, discharges, and other information. The large sample size and completeness of data is ideal for tracking patient

treatments over time and through multiple treatments[13]. Data from MarketScan contains diagnoses as well as procedure codes for every patient claim. Data from commercial inpatient, outpatient, and prescription data files from the years 2016 through 2019 were used in this analysis. Baseline characteristics were region, age, and sex.

Sample Selection

A retrospective review of the database was used to find patients who were diagnosed with metastatic esophageal cancer between 2017 and 2019. Patients were required to have at least 2 outpatient diagnoses or one inpatient diagnosis for metastatic esophageal cancer. The ICD-10 codes used in the selection of the patients can be seen in Table 4. The first qualifying esophageal cancer claim was used as the index date in the analysis. Patients were required to have continuous enrollment for a minimum of 6 months prior to the index date and for a minimum of 1 month following the index date. Data extracted from 2016 was used only to verify continuous enrollment for patients with early 2017 index dates. Claims missing an enrollment identification number, age, service data, or treatment information were excluded from the analysis.

Study Outcomes

The primary objective was to identify treatment patterns for patients with metastatic esophageal cancer. Included treatments were those indicated for chemotherapy or antineoplastic use based on the Redbook and Healthcare Common Procedure Coding System (HCPCS) J-codes. The outcome was treatment prevalence over time and common treatment pathways. Each line of therapy included all treatments given with intervals less than 21 days apart. Treatments with a gap greater than 21 days were considered a new line of therapy. In the case of combination therapies, the

removal of any single treatment within a line of therapy was not considered a new line of therapy. A line of therapy ended at the last claim for any therapy within a set combination before the beginning of a new line of therapy or as the last claim for any therapy. The duration of the therapy was calculated as the time between the first and last administration of that therapy plus a single cycle length. Cycle lengths were based on NCCN recommended cycle lengths for guideline-based therapy and on Micromedex for nonguideline based therapy.

For the secondary outcomes, a time to event analysis using the Kaplan-Meier method for treatment persistence for the 1st line of therapy and a logistic regression for odds of treatment initiation by year were performed. The start of each patient's duration for the time to event analysis began at the first claim for the first line of therapy. The end of the period for the time to event analysis was the last claim for each patient's first line of therapy plus a single cycle length. Patients were censored if they lost enrollment in their insurance. Additionally, patients were separated into those who received a single line of therapy and those who received at least 2 lines of therapy.

For the regression of treatment initiation by year, the year 2017 was used as the base year for analyzing differences between years. All patients were included in the regression analysis including patients who did not receive any treatments. The regression equation used in the analysis is listed below.

$$Logit(p) = B0 + B1X_{2018} + B2X_{2019}$$

Results

In total, 190 patients were identified who matched eligibility criteria. Figure 2 shows progression of patient counts refined sequentially by selection criteria. The mean age of all patients was 56.6 years with a standard deviation of 6.9 years. The majority (81.1%) of patients were male. The regions and other demographic information of the identified patients can be seen in Table 1. Out of the 190 patients identified in the study, 70 did not receive any treatments for esophageal cancer. The characteristics of these 70 patients can be seen in Table 2.

The treatment pattern analysis resulted in 52 different treatment combinations being identified across 4 lines of therapy and 120 patients received at least a single line of therapy. The most common treatment across all lines of therapy was a combination of fluorouracil and oxaliplatin which accounted for 21.2% of all treatments. This was followed by carboplatin and paclitaxel (9.0%); and fluorouracil, oxaliplatin, and trastuzumab (6.9%). The mean duration for a treatment regardless of line of therapy was 112 days with a standard deviation of 138 days. The complete dissection of treatments by line of therapy can be seen in Table 5. The Sankey diagram shown in Figure 3 shows the flow of patient treatments by line of therapy for patients who received at least 1 line of therapy. The diagram is separated by guideline and nonguideline based therapy. No patient received more than 4 lines of therapy and a significant portion of patients were lost at each advancement in line of therapy. Of the 120 patients who had at a minimum 1 line of therapy, 44 (36.7%) patients received 2 lines of therapy, 19 (15.8%) received 3 lines of therapy, and only 5 (4.2%) received 4 lines of therapy. In addition, 26 patients in total had a claim for hospice as the place of

service. The mean duration from the index date to a claim for hospice was 184 days. Of the 26 patients who had a claim for hospice 9 were from the group of patients that received no treatments. The attributes of patients who received hospice care can be seen in Table 3.

The results of the time to event analysis for the duration of first line of therapy can be seen in Figures 4 and 5. The median duration among all patients based on the first line of therapy treatment persistence analysis was 63 days with a 95% confidence interval from 50 days to 91 days. The results were also separated by those who continued to a new line of therapy and those who receive only 1 line of therapy. The median duration of treatment for patients who received more than one line of therapy was 106 days, and the median for patients who did not receive a new line of therapy was 49 days. The results of the logistic regression for treatment initiation by year showed no statistically significant association between year of initiation and odds of starting treatment.

Discussion

In this descriptive analysis, treatment patterns in metastatic esophageal cancer were examined by extracting data from the IBM MarketScan database for the years 2017, 2018, and 2019. The results of the treatment pattern analysis clearly show that a combination of fluorouracil and oxaliplatin is the most common first line treatment followed carboplatin and paclitaxel as well as other combinations of commonly used chemotherapy agents. The median duration of first line of therapy was 63 days and varied substantially between patients who went on to receive more than one line of

therapy versus those who did not. The year of diagnosis had no association with whether or not treatment was received.

Examining the treatment patterns plotted in Figure 3 and the lines of therapy shown in Table 5 leads to several observations. The most discernible pattern is that very few patients received multiple lines of therapy. In addition, many of the treatments being used in the 3rd and 4th lines of therapy are single agent therapies that appear in earlier combinations. This underscores the relatively poor prognosis for metastatic esophageal cancer and the lack of medications with a positive benefit to toxicity profile. The rapid decrease in patients between lines of therapy suggests that some patients may have opted for clinically trials or to discontinue further treatment. Furthermore, guideline-based therapy increased in popularity with every additional line of therapy, and no patients received treatment outside of NCCN guidelines by the 4th line of therapy. This would indicate that there are few treatments which form the foundation of therapy in metastatic esophageal cancer and new medications are needed. A new medication which is effective and with relatively low toxicity has the potential to be used at every line of therapy.

The treatment persistence curves showed a considerably longer duration of median treatment for patients who received additional lines of therapy compared to those who did not. Figures 4 and 5 and the treatment persistence curve statistics in Table 7 clearly show the difference in these patient populations. Furthermore, the 95% confidence interval for the median duration in each group do not intersect. One possible explanation for this result is that healthier patients stayed on therapy longer and were able to receive additional therapies. Another potential explanation is that patients who

experienced toxicity on their first line of therapy were unable or unwilling to receive additional treatments. Further investigation is required to fully dissect any clinical explanations for this outcome.

The logistic regression showed no association between year and probability of receiving initial treatment. This regression was performed to account for changes in medication approvals and guidelines over the study period, but the lack of a significant findings indicates that the index date had limited effect on treatment initiation. This outcome is not unexpected, but it does lead to the question of why approximately one third of the patients in each year are not receiving treatment. Patients may be declining treatment based on the severity of the disease or other factors and opting for palliative treatment. However, few patients (13.7%) had a claim originating from a hospice facility which seems to refute any palliative care justifications. Another reasonable explanation is that despite medication approvals and changes in guidelines no treatment was available that showed a positive risk-benefit analysis to the treating physicians. These results urge for additional analysis on why patients are not receiving treatment and the clinical reasoning that surrounds that decision.

Comparison

The most common treatment shown in this analysis was fluorouracil and oxaliplatin. This treatment is often given in 14-day cycles and in combination with leucovorin. This 3-part treatment is commonly known as FOLFOX. A study by Le et al. examined treatment patterns in advanced gastroesophageal and gastric cancers using the Flatiron Health database. The study found that the most common treatment in the first line of therapy to be FOLFOX which is consistent with the treatment patterns

reflected in the present study. Overall, the study by Le et al. found that of the 3291 original patients 75% received at least one line of therapy, 32% received at least two lines of therapy, 14% received at least three lines of therapy, and only 6% received at least 4 lines of therapy.[7]

Another recent study in advanced gastric cancer from Australia, Canada, Italy, and UK published in May of 2020 found that patients commonly begin with first line therapy involving either double or triple therapy based on fluoropyrimidine along with a platinum agent and/or anthracycline. Patients who required additional treatment changed to irinotecan and/or taxanes which are recommended systemic therapies for esophageal cancer. The study in gastric cancer required at least two lines of therapy as an inclusion criterion; however, only 29.6% of the 280 patients received a third line of chemotherapy. [3,5] In the present study 15.8% received 3 lines of therapy, and 4.2% received 4 lines of therapy. This is a rather large discrepancy in the rate of 3rd line therapy for advanced cancer. The most likely answer for this is the site of the cancer itself and differences in the pathologies, but further investigation is needed.

Limitations

There are several limitations which may have affected the outcome of this study. The first is the MarketScan database itself and the data used in the analysis. The database contains primarily claims from individuals with private insurance which results in a sample of patients that is likely to be under the age of 65. In addition, this convenience sample is limited by not collecting data from patients who have public insurance based on age, income, or disabilities. Another limitation is the length of the study. The study utilized data from 2016 through 2019, but a longer sample period

would have resulted in more patients and a larger pattern analysis. An additional limitation was the assembly of the lines of therapy based on treatment times and claims service dates. The lines of therapy were assembled based on a standardized time which may not accurately reflect the administration of every medication; especially, unique or unusual treatments.

Future Studies

Additional research should be conducted in understanding treatment patterns in esophageal cancer. Statistical comparison of patterns in MarketScan compared to other databases needs to be conducted to verify the accuracy of the patterns found in this study. Additional analysis comparing patients who received guideline-based therapy and those who did not needs to be performed to fully quantify the effect of non-approved treatments. In addition, the current study should be continued to analyze patterns from 2020 and 2021 when data from these years becomes available, but continued analysis should heavily consider the effect of the COVID-19 pandemic.

Conclusion

The final conclusions that can be drawn from this study are that many medications and combinations are used when treating metastatic esophageal cancer. Most of these treatments are based on guidelines and a few therapies form the foundation of treatment in this population. A substantial number of patients did not initiate any therapy regardless of year of diagnosis. The culmination of these different pieces of evidence shows that there is room for innovation and improvement on current recommended treatments.

Tables

Table 1. Baseline Demographic Information

	2017 (N=64)	2018 (N=59)	2019 (N=67)	Overall (N=190)
Region				
Northeast	16 (25.0%)	11 (18.6%)	13 (19.4%)	40 (21.1%)
North Central	14 (21.9%)	15 (25.4%)	19 (28.4%)	48 (25.3%)
South	23 (35.9%)	23 (39.0%)	27 (40.3%)	73 (38.4%)
West	11 (17.2%)	10 (16.9%)	7 (10.4%)	28 (14.7%)
Unknown	0 (0%)	0 (0%)	1 (1.5%)	1 (0.5%)
AGE (years)				
Mean (SD)	58.0 (5.63)	56.5 (6.82)	55.4 (7.79)	56.6 (6.88)
Median [Min, Max]	60.0 [39.0, 65.0]	57.0 [30.0, 65.0]	57.0 [28.0, 64.0]	58.5 [28.0, 65.0]
Sex				
Male	52 (81.2%)	50 (84.7%)	52 (77.6%)	154 (81.1%)
Female	12 (18.8%)	9 (15.3%)	15 (22.4%)	36 (18.9%)

Table 2. Demographic Information for Patients Who Received No Treatments

	2017 (N=24)	2018 (N=17)	2019 (N=29)	Overall (N=70)
Region				
Northeast	9 (37.5%)	4 (23.5%)	3 (10.3%)	16 (22.9%)
North Central	6 (25.0%)	2 (11.8%)	8 (27.6%)	16 (22.9%)
South	5 (20.8%)	7 (41.2%)	17 (58.6%)	29 (41.4%)
West	4 (16.7%)	4 (23.5%)	0 (0%)	8 (11.4%)
Unknown	0 (0%)	0 (0%)	1 (3.4%)	1 (1.4%)
AGE (years)				
Mean (SD)	59.2 (4.83)	54.9 (6.96)	55.1 (8.36)	56.5 (7.17)
Median [Min, Max]	61.0 [48.0, 65.0]	56.0 [32.0, 62.0]	57.0 [28.0, 64.0]	58.0 [28.0, 65.0]
Sex				
Male	19 (79.2%)	13 (76.5%)	22 (75.9%)	54 (77.1%)
Female	5 (20.8%)	4 (23.5%)	7 (24.1%)	16 (22.9%)

Table 3. Demographic Information for Patients Who Received Hospice Care

	Overall (N=26)
Region	
Northeast	2.00 (7.7%)
North Central	7.00 (26.9%)
South	14.0 (53.8%)
West	2.00 (7.7%)
Unknown	1.00 (3.8%)
AGE (days)	
Mean (SD)	57.7 (6.71)
Median [Min, Max]	59.5 [39.0, 64.0]
Sex	
Male	25.0 (96.2%)
Female	1.00 (3.8%)
Days Before Hospice	
Mean (SD)	184 (151)
Median [Min, Max]	187 [0, 466]

Table 4. ICD-10 Codes Used for Identifying Eligible Patients

Diagnosis	ICD-10
Malignant neoplasm of esophagus	C15.X
Malignant neoplasm of upper third of esophagus	C15.3
Malignant neoplasm of middle third of esophagus	C15.4
Malignant neoplasm of lower third of esophagus	C15.5
Malignant neoplasm of overlapping sites of esophagus	C15.8
Malignant neoplasm of esophagus, unspecified	C15.9

Table 5. Treatments by Line of Therapy

	LOT1 (N=120)	LOT2 (N=44)	LOT3 (N=19)	LOT4 (N=5)	Overall (N=189)
Treatment					
Anastrozole	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Capecitabine	9 (7.5%)	2 (4.5%)	1 (5.3%)	0 (0%)	12 (6.3%)
Capecitabine, Cisplatin, Trastuzumab	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Capecitabine, Oxaliplatin	1 (0.8%)	1 (2.3%)	0 (0%)	0 (0%)	2 (1.1%)
Capecitabine, Oxaliplatin, Trastuzumab	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Carboplatin, Docetaxel, Fluorouracil	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Carboplatin, Etoposide	2 (1.7%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)
Carboplatin, Fluorouracil, Oxaliplatin	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Carboplatin, Paclitaxel	11 (9.2%)	4 (9.1%)	2 (10.5%)	0 (0%)	17 (9.0%)
Carboplatin, Paclitaxel, Trastuzumab	2 (1.7%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)
Cisplatin, Docetaxel, Fluorouracil	3 (2.5%)	0 (0%)	0 (0%)	0 (0%)	3 (1.6%)
Cisplatin, Fluorouracil, Trastuzumab	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Cisplatin, Irinotecan	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Dabrafenib Mesylate, Trametinib Dimethyl Sulfoxide	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Docetaxel, Fluorouracil	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Docetaxel, Fluorouracil, Oxaliplatin	2 (1.7%)	1 (2.3%)	1 (5.3%)	0 (0%)	4 (2.1%)
Docetaxel, Pertuzumab, Trastuzumab	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Exemestane	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Fluorouracil	1 (0.8%)	2 (4.5%)	1 (5.3%)	0 (0%)	4 (2.1%)
Fluorouracil, Oxaliplatin	26 (21.7%)	9 (20.5%)	4 (21.1%)	1 (20.0%)	40 (21.2%)
Fluorouracil, Oxaliplatin, Trastuzumab	10 (8.3%)	3 (6.8%)	0 (0%)	0 (0%)	13 (6.9%)
Ipilimumab, Nivolumab	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Irinotecan	5 (4.2%)	1 (2.3%)	0 (0%)	0 (0%)	6 (3.2%)
Irinotecan, Ramucirimab	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Lenvatinib	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Letrozole, Palbociclib	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Megestrol Acetate	4 (3.3%)	3 (6.8%)	1 (5.3%)	1 (20.0%)	9 (4.8%)
Mercaptopurine, Methotrexate Sodium	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Nivolumab	1 (0.8%)	1 (2.3%)	1 (5.3%)	0 (0%)	3 (1.6%)
Oxaliplatin	1 (0.8%)	1 (2.3%)	0 (0%)	0 (0%)	2 (1.1%)
Oxaliplatin, Trastuzumab	2 (1.7%)	0 (0%)	1 (5.3%)	0 (0%)	3 (1.6%)
Paclitaxel	3 (2.5%)	1 (2.3%)	0 (0%)	0 (0%)	4 (2.1%)
Paclitaxel, Ramucirimab	6 (5.0%)	3 (6.8%)	1 (5.3%)	0 (0%)	10 (5.3%)
Palbociclib	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Palbociclib, Tamoxifen Citrate	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Pembrolizumab	4 (3.3%)	3 (6.8%)	2 (10.5%)	0 (0%)	9 (4.8%)
Ramucirimab	4 (3.3%)	0 (0%)	0 (0%)	0 (0%)	4 (2.1%)
Trastuzumab	5 (4.2%)	2 (4.5%)	0 (0%)	0 (0%)	7 (3.7%)
Capecitabine, Epirubicin, Oxaliplatin	0 (0%)	1 (2.3%)	0 (0%)	0 (0%)	1 (0.5%)
Carboplatin, Pembrolizumab, Pemetrexed	0 (0%)	1 (2.3%)	0 (0%)	0 (0%)	1 (0.5%)
Cobimetinib, Vemurafenib	0 (0%)	1 (2.3%)	0 (0%)	0 (0%)	1 (0.5%)
Everolimus, Lenvatinib	0 (0%)	1 (2.3%)	0 (0%)	0 (0%)	1 (0.5%)
Irinotecan, Trastuzumab	0 (0%)	1 (2.3%)	0 (0%)	0 (0%)	1 (0.5%)
Pazopanib Hydrochloride	0 (0%)	1 (2.3%)	0 (0%)	0 (0%)	1 (0.5%)
Tamoxifen Citrate	0 (0%)	1 (2.3%)	0 (0%)	0 (0%)	1 (0.5%)
Capecitabine, Irinotecan	0 (0%)	0 (0%)	1 (5.3%)	0 (0%)	1 (0.5%)
Everolimus, Letrozole, Megestrol Acetate	0 (0%)	0 (0%)	1 (5.3%)	0 (0%)	1 (0.5%)
Fluorouracil, Irinotecan	0 (0%)	0 (0%)	1 (5.3%)	0 (0%)	1 (0.5%)
Temozolomide	0 (0%)	0 (0%)	1 (5.3%)	0 (0%)	1 (0.5%)
Capecitabine, Lapatinib Ditosylate	0 (0%)	0 (0%)	0 (0%)	1 (20.0%)	1 (0.5%)
Fluorouracil, Megestrol Acetate, Oxaliplatin	0 (0%)	0 (0%)	0 (0%)	1 (20.0%)	2 (1.1%)
Osimertinib	0 (0%)	0 (0%)	0 (0%)	1 (20.0%)	1 (0.5%)
Duration (days)					
Mean (SD)	122 (138)	89.8 (98.5)	115 (212)	78.6 (67.1)	112 (138)
Median [Min, Max]	73.0 [7.00, 973]	48.5 [7.00, 358]	63.0 [14.0, 966]	62.0 [7.00, 168]	63.0 [7.00, 973]

Table 6. Proportion of Treated Patients by Year

	2017 (N=64)	2018 (N=59)	2019 (N=67)	Overall (N=190)
Proportion Treated				
Mean (SD)	0.63 (± 0.49)	0.71 (± 0.46)	0.57 (± 0.50)	0.63 (± 0.48)

Table 7. Treatment Persistence Curve Statistics

	25% Percentile	50% Percentile	75% Percentile
Overall - Days(CI)	29 (21, 41)	63 (50, 91)	159 (126, 203)
New Treatment?			
No	21 (21, 30)	49 (35, 70)	120 (83, 169)
Yes	56 (35, 89)	106 (78, 191)	248 (168, 393)

Figures

Figure 1. Study Timeline Diagram

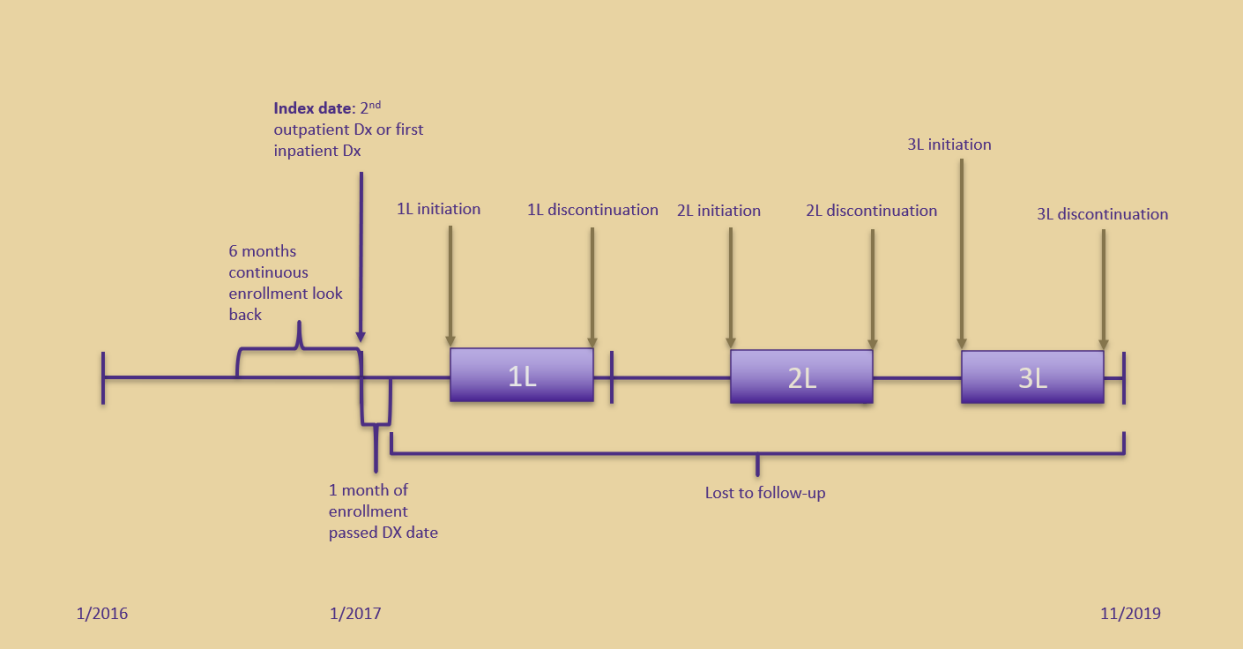


Figure 2. Patient Counts by Eligibility Criteria

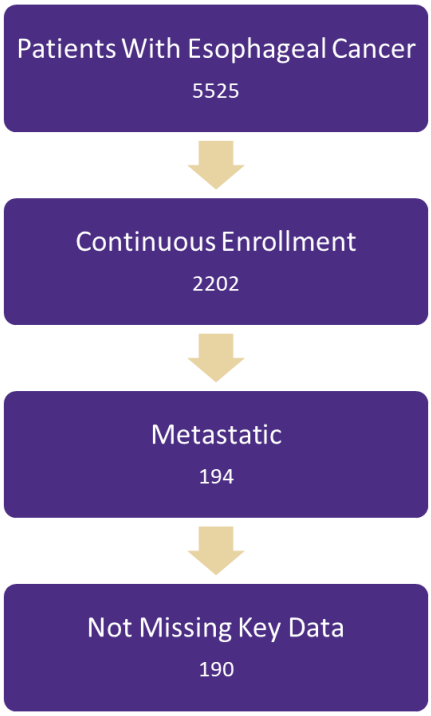


Figure 3. Treatment Patterns Separated by Inclusion in NCCN Guidelines

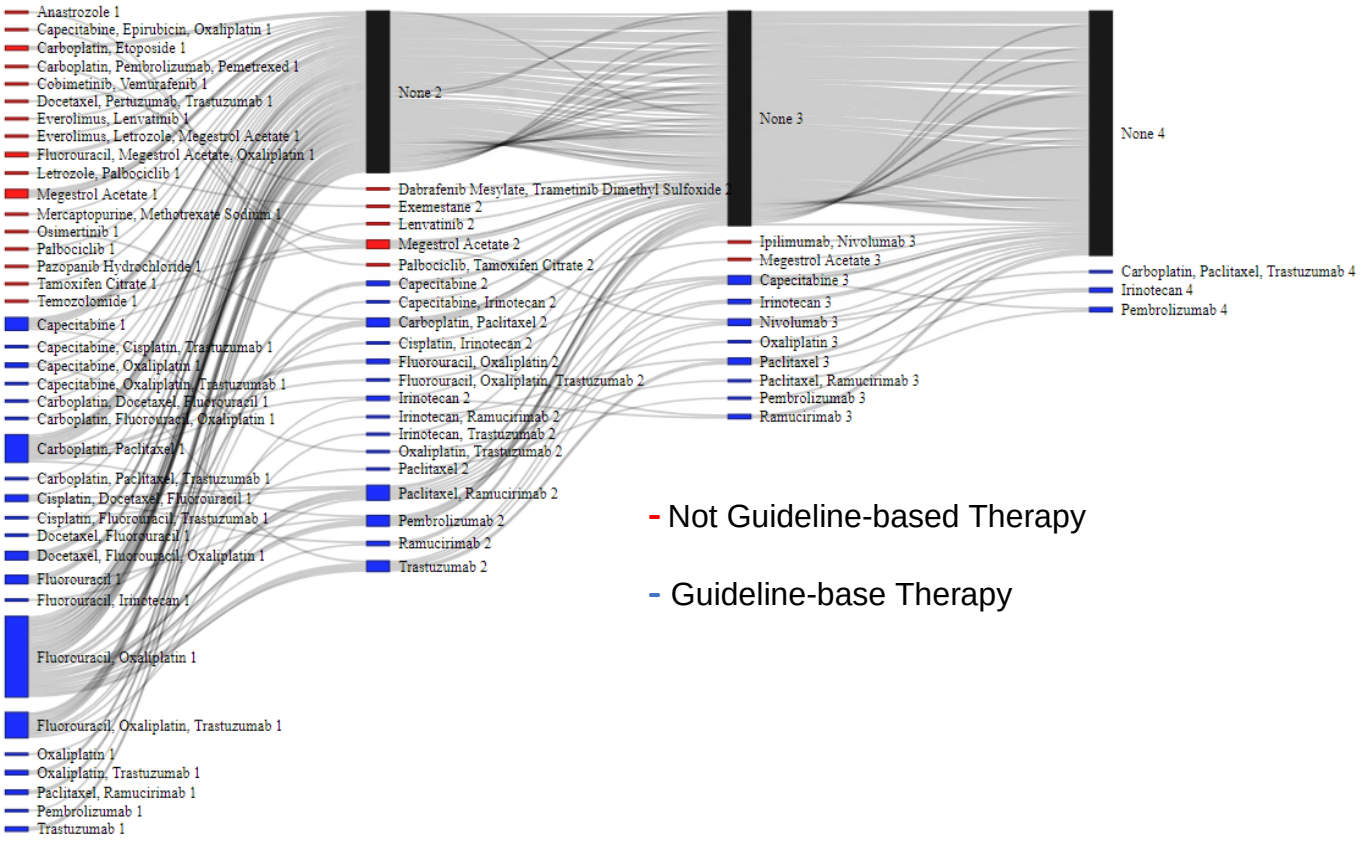


Figure 4. Treatment Persistence Curve for First Line of Therapy -All Patients

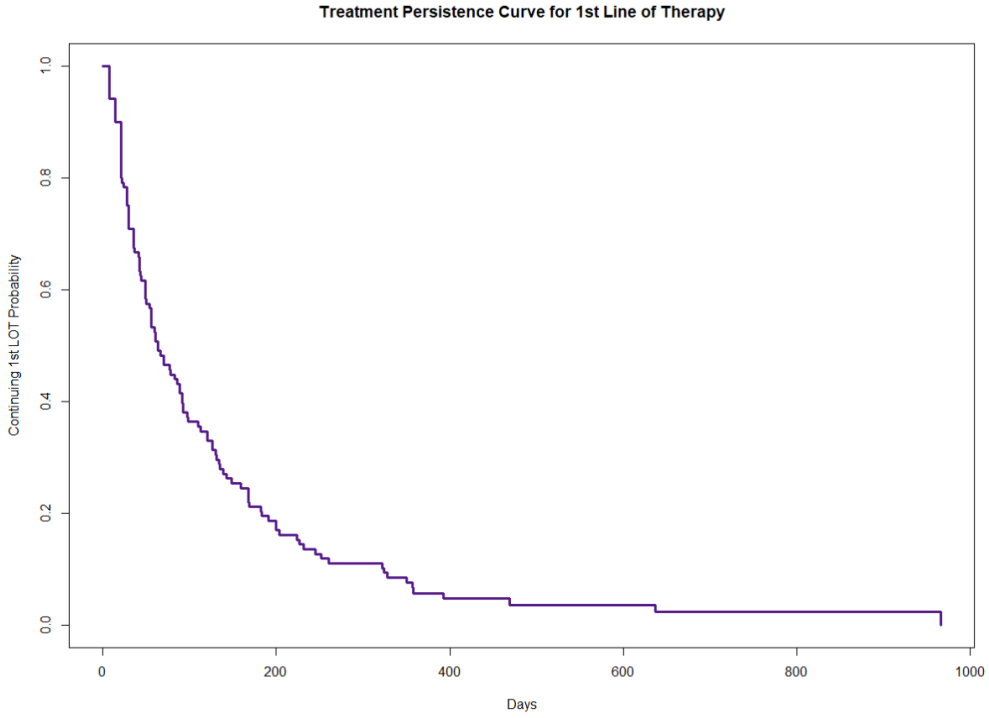
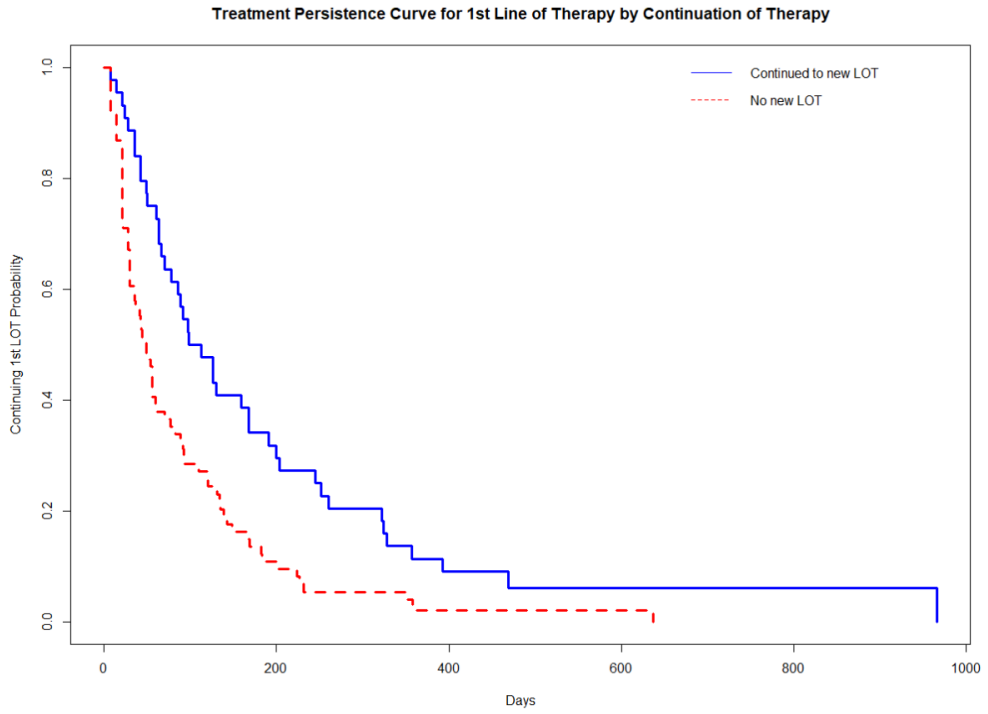


Figure 5. Treatment Persistence Curve for First Line of Therapy -Grouped by New Therapy



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