Distribution and Timing of Distant Metastasis after Local Therapy in a Large Cohort of Patients with Esophageal and Esophagogastric Junction Cancer

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Key Words

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clinical model is desirable that associates clinical parameters with a high risk for DM in TMT-eligible patients prior to surgery.

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Abstract

Background: Patients with localized esophageal and esophagogastric junction cancer (EAC) receive chemoradiation and then surgery (trimodality, TMT) or definitive chemoradiation (bimodality, BMT). Distant metastases (DMs) are common but the details of their distribution and timing in a large cohort have not been described. **Methods:** 629 patients with localized EAC who had TMT or BMT were analyzed. Standard statistical methods were used to define the end points. **Results:** The median follow-up time was 37.2 months (interquartile range 17.8–65.0). Of 356 TMT patients, 33% (119) developed DM as their first relapse and of 273 BMT patients, 40% (109) developed DM; 91% (TMT) and 96% (BMT) of the DMs were diagnosed within 2 years of local therapy. The most common sites of DM were: lung, distant nodes, liver, peritoneal cavity, bone, brain and pleura in order of frequency. The median overall survival of TMT patients with DM was 10.2 months (95% CI 7.8–12.7) and that for BMT patients with DM was 7.8 months (95% CI 5.7–9.9). **Conclusions:** Following TMT or BMT, ≥33% of patients developed DMs and most of these occurred within 2 years (>90%) of local therapy. A

Introduction

Patients with esophageal and/or esophagogastric junction cancer (EAC) often have poor prognosis even when the cancer is localized. The incidence of EAC continues to rise in the USA; in 2013, an estimated 17,790 people were diagnosed with the disease and there were 15,210 deaths [1]. When EAC is localized, patients are treated with preoperative chemoradiation (trimodality therapy, TMT) or definitive chemoradiation (bimodality therapy, BMT) [2–4]. We reported that distant metastases (DMs) are fairly frequent after TMT and BMT [5–7]. Detailed information on the timing and exact frequency of DMs in this patient population has not been fully reported. We report here on the frequency, sites and timing of DMs in a large cohort of patients. Our ultimate goal is to develop a clinical model that will associate clinical parameters with a high likelihood of DM, prior to local therapy or surgery. If such a clinical model is established, it may provide an opportunity to properly select therapies for the high-risk subset. Currently, no such model exists.

Methods

Patients

The study cohort was identified from a prospectively maintained database at the Department of Gastrointestinal Medical Oncology, University of Texas M.D. Anderson Cancer Center, between 2002 and 2013. We included all patients with localized EAC who received TMT or BMT with a curative intent. All patients were staged by imaging study and upper endoscopic ultrasound. The therapy decision (i.e. TMT or BMT) was made at the multidisciplinary conference. The American Joint Committee on Cancer, 6th edition, was used for clinical staging. No other selection criteria were applied. The institutional review board approved this analysis.

Treatment

Chemotherapy with radiation included a fluoropyrimidine (intravenous or oral) and either a platinum compound or a taxane. Radiation with a total of 45–50.4 Gy was delivered in 1.8 Gy per fraction by one of the conformal techniques. Platinum or taxane was given 5× weekly and fluoropyrimidine was given 5× on 5 days/week. In TMT-eligible patients, an esophagectomy was performed after 6–8 weeks after the completion of chemoradiation. The primary surgeon selected the surgical technique [transthoracic (Ivor-Lewis), transhiatal, total (three-field technique) or minimally invasive esophagectomy with lymph node dissection].

Surveillance

Imaging studies and endoscopy were performed upon completion of local therapy. Additional follow-up data were obtained from our institution's tumor registry and the hospital records or the Social Security database.

Statistical Analysis

Time to DM was defined as the time from the end of local therapy. Overall survival (OS) for patients who developed DM was defined from the diagnosis of DM to death or the last follow-up. The rate of distribution and timing of relapse were tabulated by frequency and percentage. OS values were obtained by the Kaplan-Meier method. Statistical analyses were performed using SPSS software (IBM SPSS statistics 21.0).

Results

Patient Characteristics

We studied a total of 629 consecutive patients (356 who had TMT and 273 who had BMT) between 2002 and 2013. The median age was 63 years (range 20–91). Most of the patients were men (88.1%) and white (89.3%). The main primary site was the esophagogastric junction (84.9%) and the most frequent histology was adenocarcinoma (87.4%). The clinical characteristics of these patients are summarized in table 1. The median follow-up time was 37.2 months (interquartile range 17.8–65) for patients who were still alive.

Table 1. Pretreatment characteristics of the 629 patients

Covariate	Eligible patients	Percentage of total
Age, years		
Median	63	
Minimum-maximum	20–91	
Gender		
Males	554	88.1
Females	75	11.9
Race		
White	562	89.3
Others	67	10.7
Primary site		
Esophagus	95	15.1
EGJ	534	84.9
Histology		
Adenocarcinoma	550	87.4
Squamous cell carcinoma	79	12.6
Histological grade		
Well-moderate	298	47.4
Poorly	331	52.6
Baseline T stage		
T ₁	11	1.7
T ₂	64	10.2
T ₃	537	85.4
T ₄	17	2.7
Baseline N stage		
N ₀	221	35.1
N ₁	408	64.9
Baseline M stage		
M ₀	614	97.6
M _{1a}	15	2.4
Baseline stage		
Stage I	10	1.6
Stage II	236	37.5
Stage III	368	58.5
Stage IVA	15	2.4

Figures represent the number of patients, unless otherwise specified. EGJ = Esophagogastric junction.

Patterns of Failure

The patterns of failure are summarized in figure 1. Forty percent (144 of 356 patients) who had TMT and 64% (175 of 273 patients) who had BMT had a relapse. Of 144 relapses after TMT and 175 after BMT, 83 and 62%, respectively, were DM.

Distribution and Timing of DM

The 7 most common anatomical sites of DM, as the first exclusive event, were the lung (for TMT 20% and for BMT 17%), distant lymph nodes (13 and 20%), liver (14 and 11%), peritoneum (10 and 13%), bone (6 and 11%), brain (8% in both groups) and pleura (7 and 5%). The cu-

Fig. 1. Patterns of failure after TMT and BMT for EAC. LF = Luminal-only failure; RF = regional failure.

Table 2. Duration-specific rate of all of DM (in months) from completion of treatment

	0–12	13–24	25–36	37–48	49–60	Total
DM following 356 TMT procedures	87	21	8	2	1	119
*	24.4%	5.9%	2.2%	0.6%	0.3%	33.4%
**	73.1%	17.6%	6.7%	1.7%	0.8%	100.0%
***	73.1%	90.8%	97.5%	99.2%	100.0%	
DM following 273 BMT procedures	93	12	3	0	1	109
*	34.1%	4.4%	1.1%	0.0%	0.4%	39.9%
**	85.3%	11.0%	2.8%	0.0%	0.9%	100.0%
***	85.3%	96.3%	99.1%	99.1%	100.0%	

Duration-specific rate of DM from completion of treatment (months).

* Denominators are the number of patients with each treatment; 356 with TMT and 273 with BMT.

** Denominators are the number of DMs in each treatment; 119 with TMT and 109 with BMT.

*** Cumulative % of failure.

ulative rates of DM were 90.8 and 96.3% after TMT and BMT within 2 years after the completion of treatment and 97.5 and 99.1% after TMT and BMT within 3 years, respectively (table 2).

Overall Survival after DM

The median OS time of the total of DM was 10.2 months (95% CI 7.8–12.7) for TMT patients and 7.8 months (95% CI 5.7–9.9) for BMT patients. Those with pleural DM had the shortest OS: 1.5 months (95% CI 1.0–2.1) for TMT and 3.5 months (95% CI 3.3–3.6) for BMT.

Discussion

Our analysis, representing the largest cohort of patients to date, demonstrates that DM as a first sign of relapse after local therapy of EAC patients is common. The TMT patients, with relatively less-advanced local EAC had a slightly lower frequency of DM compared to the BMT patients who more often had advanced local EAC. It is, of course, disappointing if a TMT patient develops DM (especially within 12 months of surgery). If we can identify patients who are destined to develop

DM, we may be able to change the clinical algorithm (e.g. delay surgery for a certain period of time if the risk for DM is high); however, it is unclear what could be done for BMT patients destined to develop DM (prolonged induction systemic therapy?). Currently, there is no clinical or biomarker model associated with a high likelihood of the development of DM. Such a model would be desirable to explore various clinical approaches.

This study is retrospective and has all the limitations of a retrospective analysis. A strength of the study is that it has the largest number of patients ever reported for characterizing DM.

In conclusion, our data show that DM is a common occurrence after local therapy of patients with EAC. A clinical variables' model to predict DM would be desirable.

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Disclosure Statement

The authors have no financial or any other conflict of interest.

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