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ORIGINAL ARTICLE

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Retrospective analysis of disease characteristics and treatment patterns among patients with esophageal cancer across 14 surgically represented centers

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ABSTRACT

Objective: Esophageal cancer (EC) ranks eighth among cancers in cancer-related deaths globally, and ~44% of new cases occur in China. We sought to describe the clinical characteristics and treatment landscape of EC in China before the approval of immunotherapy in 2020.

Methods: CHANNEL was a large, retrospective study using patient-level data from 14 hospitals/cancer centers across China, including adults initiating therapy for newly diagnosed EC (January to December 2018). Demographics, clinicopathologic characteristics, and treatment patterns over 6 months were descriptively summarized.

Results: Of 3,493 patients, 75.7% were men, the mean age was 64.1 years, and 75.0% had no family history of cancer. Most (92.8%) had squamous cell carcinoma, with a primary lesion in the middle esophagus (56.4%). Among patients with resectable EC, 92.9% received initial surgery, and 7.1% received neoadjuvant therapy, primarily chemotherapy (85.5% platinum-taxane). Among patients with unresectable early or locally advanced EC, 50.8% and 49.2% received palliative and radical therapy, respectively, as the initial treatment, primarily chemotherapy (66.5% platinum-taxane) and chemoradiotherapy (50.8% platinum-taxane), respectively. Adjuvant therapy was administered to 22.9% of patients undergoing initial surgery, and 2.4% receiving neoadjuvant therapy and surgery. Among patients with advanced EC, 84.6% received systemic therapy as an initial treatment, primarily chemotherapy (61.5% platinum-taxane).

Conclusions: Before the approval of immunotherapy in China, most patients with resectable early or locally advanced EC underwent radical surgery without preoperative treatment, whereas most patients with advanced EC received platinum-taxane chemotherapy. These findings highlight the need for novel EC treatments before immunotherapy was introduced, and provide a baseline for evaluating the benefits of immunotherapy, now that this treatment is widely used in this setting.

KEYWORDS Esophageal cancer; China; clinicopathologic characteristics; treatment landscape; retrospective

Introduction

Esophageal cancer (EC) is the eighth most common cause of cancer-related death globally[1]. China has the highest incidence of new EC cases of any country, and currently accounts for ~44% of total new EC cases worldwide[1]. Squamous cell carcinoma is the predominant histological EC subtype in China and Asia (> 90% of cases in China), whereas in Western countries, adenocarcinoma is more common[2-5]. EC is observed in a higher proportion of female patients in Asian countries than Western countries[6], and differences in the risk factors for developing EC, disease stage at diagnosis, molecular epidemiology, and sensitivity to treatment have been observed[7]. EC of squamous cell and adenocarcinoma histology is characterized by differing etiologies, risk factors, and clinical characteristics, and also requires different treatment approaches[8]. Additional differences in the characteristics of EC exist among Asian countries, for example China and Japan[9].

The clinical management of EC typically includes surgery, radiotherapy, or chemoradiotherapy for early-stage and potentially resectable disease, or systemic therapy for unresectable advanced or metastatic cancer[5,10,11]. Before the introduction of immunotherapy for EC in 2020, the standard neoadjuvant treatment for patients with resectable EC was chemoradiotherapy, combined with targeted therapies in patients with specific molecular aberrations[5]. However, chemotherapy alone is associated with suboptimal survival response rates and safety concerns, and not all patients with EC bear other targetable mutations[12-14]. Therefore, immunotherapy has provided an important additional treatment option for a large proportion of patients with EC, particularly in Asia, where squamous cell carcinoma is highly prevalent[6].

Two immunotherapy agents, pembrolizumab and nivolumab, are approved globally for the treatment of EC, both of which have been shown to improve survival outcomes in patients with advanced EC, as a first-line treatment combined with chemotherapy (approved in 2021 and 2022, respectively) and a second-line treatment as monotherapy (approved in 2019 and 2020, respectively)[10,15-17]. In China, pembrolizumab was the first agent for immunotherapy approved in the first-line (2021) and second-line (2020) for treatment of advanced EC[18]. In addition, nivolumab and several locally produced immunotherapy drugs are approved for the treatment of EC[19-23]. Perioperative immunotherapy has also been shown to benefit select patients[10].

Understanding EC treatment patterns in China before the introduction of immunotherapy is crucial for evaluating the resultant changes in EC management. In particular, the types of chemotherapy used in combination with immunotherapy differ in Asia and China *vs.* Western countries, with wider use of paclitaxel in East Asia, especially China[24,25]. However, data on the clinical features and treatment patterns for EC before the approval of immunotherapy in China are scarce, and prior studies have generally included relatively small numbers of patients from single centers[26-29], thus limiting the generalizability of the findings to the wider Chinese population. A large-scale study is therefore required to evaluate the treatment landscape for EC before the approval of immunotherapy, to provide a baseline for future analyses. Such a study would also enhance understanding of the clinicopathologic features of EC in patients in China and identify data gaps and unmet medical needs in this population.

The CHANNEL study was a large, nationwide, multicenter, retrospective study aimed at describing the clinical features and treatment patterns of EC in China before immunotherapy approval. These data provide a foundation for exploring the correlation between immunotherapy and EC and its effects on patient outcomes.

Materials and methods

Data source and study design

This retrospective analysis was conducted on patient-level data collected from electronic medical records (EMRs) from 14 large hospitals and cancer centers across various geographic regions in China (**Table 1**). Patients who initiated first-line therapy for newly diagnosed EC between January 1, 2018, and December 31, 2018, were identified. The start date of this initial treatment was designated as the index date. EMRs were consecutively screened, beginning from the earliest index date and progressing in reverse to the most recent index date. Data on demographics, clinicopathologic characteristics, and anti-tumor treatment patterns for as many as 6 months after the index date were obtained and descriptively summarized.

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Table 1 Study centers and patient enrollment

Patients, *n* (%)	Total screened (*n* = 4,036)	Total enrolled (*n* = 3,493)
01. Peking University Cancer Hospital & Institute	215 (5.3)	205 (5.9)
02. Anyang Cancer Hospital	664 (16.5)	608 (17.4)
03. Sichuan Cancer Hospital	451 (11.2)	440 (12.6)
06. Harbin Medical University Cancer Hospital	334 (8.3)	203 (5.8)
07. Weifang Second People's Hospital	25 (0.6)	24 (0.7)
08. Shandong Cancer Hospital	256 (6.3)	219 (6.3)
09. The First Affiliated Hospital of Xi'an Jiaotong University	274 (6.8)	132 (3.8)
10. Nanyang Central Hospital	254 (6.3)	192 (5.5)
12. Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology	290 (7.2)	251 (7.2)
15. The Fourth Hospital of Hebei Medical University	335 (8.3)	331 (9.5)
16. Zhongshan Hospital, Fudan University	304 (7.5)	293 (8.4)
17. Affiliated Hospital of Jiangsu University	200 (5.0)	198 (5.7)
18. The First Affiliated Hospital of Xinjiang Medical University	54 (1.3)	51 (1.5)
20. Shanxi Provincial Cancer Hospital	380 (9.4)	346 (9.9)

Preliminary screening of 4,036 eligible patients from the database according to the inclusion criteria, 3,493 of whom were enrolled.

The CHANNEL study protocol was approved by an institutional review board/independent ethics committee (IRB/IEC) at each study site before study initiation. The study was registered on EU PAS (register number: EUPAS48396).

Study population

Eligible patients were ≥ 18 years of age at EC diagnosis and had histologically or cytologically confirmed EC regardless of stage (including advanced or metastatic, early-stage, or locally advanced), had not received prior treatment for EC, and received the first anti-tumor treatment for EC during the eligibility period at the corresponding study site. All patients provided a signed informed consent form to participate in the study, or had conditions accepted by the IRB/IEC to waive this requirement. Patients were excluded if they had multiple primary cancers indicated in the EMR, or had participated in any investigational program or clinical trial involving interventions outside routine clinical practice for anti-tumor purposes.

Enrolled patients were classified into early, locally advanced, or advanced stage EC groups. Early-stage EC was defined as T1N0M0; locally advanced EC was defined as M0 and T2 or N+; and advanced EC with metastatic disease was defined as M1.

Outcomes and measurements

The primary outcomes of this analysis were the clinicopathological features and initial treatment patterns of the patients with EC. Subsequent treatment patterns (second line and beyond) were evaluated as a secondary outcome.

Demographics

The collected demographic data included age at EC diagnosis, gender, residential area, smoking and alcohol consumption history, and family history of cancer.

Clinicopathological features

The recorded clinicopathological variables included the location of the primary tumor site; histology and tumor grade; tumor stage; presence and location of distant metastases; and information on any biomarkers tested as part of the patient's clinical management, including programmed cell death ligand 1 (PD-L1), epidermal growth factor receptor (EGFR), and human epidermal growth factor receptor 2 (HER2).

Treatment patterns

Treatments were classified into initial or subsequent lines of therapy. Initial treatment was defined as the first treatment approach received after EC diagnosis, and included multiple cycles or doses of the same anti-cancer therapy. Subsequent treatment referred to any new treatment (i.e., received after the initial treatment had been completed or discontinued) within 6 months after the start of the initial treatment.

Initial treatment patterns were described by disease status (early-stage, locally advanced, or advanced). Categories of treatment comprised surgery, neoadjuvant or adjuvant therapy, curative therapy, and palliative therapy; and treatments included radiotherapy, chemoradiotherapy, chemotherapy, and targeted therapies.

When disease recurrence occurred in patients with early-stage or locally advanced EC, similar variables to those recorded for the initial treatment were recorded for the subsequent treatment, on the basis of patients' current disease status, including the date and type of recurrence (local, regional, or distant). For patients with advanced EC receiving systemic therapy, subsequent treatments after disease progression were documented.

Statistical analysis

All variables were summarized descriptively. Continuous variables were summarized with mean, median, range, and standard deviation, and categorical variables were analyzed with frequency distributions.

The initial treatment modality (surgery, radiotherapy, or systemic therapy) was recorded. Surgery type, dose of radiation, and number of chemoradiotherapy cycles were assessed. For each initial systemic treatment, the regimen (reported by class only), median duration of therapy, and median number of cycles administered were summarized. Similarly, the proportion of patients receiving subsequent treatments was recorded, together with the modality, treatment regimen, and number of cycles administered. Second- and third-line systemic therapies were analyzed separately. The frequency of recurrence after curative treatment and progression after systemic treatment were also recorded.

No tests of statistical significance were included in this study; 95% confidence intervals were calculated with the Clopper–Pearson method.

Results

Study population and clinicopathologic features

A total of 4,036 patients with EC were screened, among whom 3,493 patients from 14 hospitals met the eligibility criteria and were included (**Table 1**). The main reasons for exclusion were the presence of multiple primary tumors, missing information on treatment modality, and previous treatment. The overall screening failure rate was 13.5%. Most patients were men (75.7%), with a mean age of 64.1 years at diagnosis, and lived in an urban area (53.4%) (**Table 2**). A total of 75.0% of patients had no family history of cancer. Among 3,199 patients with available data, 2,142 had resectable disease [early-stage, n = 429 (13.4%); locally advanced, n = 1,713 (53.5%)], 828 (25.9%) had unresectable disease, and 229 (7.2%) had advanced-stage disease.

At baseline, most patients had squamous cell carcinoma (92.8%), with the primary lesion located in the middle esophagus (56.4%) (**Table 2**). The proportion of patients with TNM stage I, II, III, and IV disease was 14.7%, 31.2%, 38.6%, and 15.4%, respectively. Among 229 (7.1%) patients with distant metastases at baseline, the most common affected location was the lymph nodes [39 (55.7%) of patients based on non-missing data]. Biomarker data were available for only 67 (1.9%) patients.

Initial treatment patterns

Among the 2,142 patients with resectable EC, 1,989 (92.9%) underwent initial radical surgery (primarily esophagectomy, 99.2%), and 153 (7.1%) received neoadjuvant therapy (**Table 3**). The mean time from diagnosis to surgery was approximately 2 weeks. Chemotherapy was the most commonly used neoadjuvant therapy (85.6%) and was primarily platinum-based, most frequently platinum + taxane (85.5%).

For the 828 patients with unresectable early or locally advanced EC, the initial treatment comprised radical therapy in 49.2% of patients, including definitive chemoradiotherapy (31.7%) and radiotherapy (17.5%) (**Table 4**). The most prevalent radical chemoradiotherapy regimens were platinum + taxane (50.8%) and platinum + pyrimidines (10.3%). Patients treated with chemoradiotherapy received a median total radiation dose of 64.00 (Q1: 60.00, Q3: 116.00) Gy delivered over a median of 2.0 (range 1–9) chemoradiotherapy cycles.

Table 2 Patient demographics and baseline clinicopathologic characteristics

Variable*	Patients (*n* = 3,493)
Gender	
Male	2,644 (75.7)
Age at EC diagnosis, mean, years (SD)	64.1 (8.4)
Residential area[†, ‡]	
Urban	1,710 (53.4)
Rural	1,494 (46.6)
Smoking status[‡]	
Current/former smoker	1,838 (52.6)
Never smoked	1,640 (47.2)
Alcohol drinking status[‡]	
Current/former drinker	1,530 (43.8)
Never been a drinker	1,898 (55.4)
Family history of cancer	
Yes	873 (25.0)
Primary EC tumor site[‡]	
Upper	625 (17.9)
Middle	1,966 (56.4)
Lower	1,438 (41.2)
Junctional	68 (1.9)
Histology[‡]	
Squamous cell carcinoma	3,242 (92.8)
Adenocarcinoma	109 (3.1)
Adenosquamous cell carcinoma	5 (0.1)
Neuroendocrine carcinoma	41 (1.2)
Other cell types	95 (2.7)
Tumor grade[‡]	
G1 (well differentiated)	224 (6.4)
G1 (moderately differentiated)	1,300 (37.4)
G3 (poorly differentiated)	697 (20.1)
G4 (undifferentiated)	4 (0.1)
Gx (grade cannot be assessed)	1,251 (36.0)
TNM stage[‡,§]	
0	3 (0.1)
I	472 (14.7)
II	999 (31.2)
III	1,239 (38.6)
IV	5 (0.2)
IVa	260 (8.1)
IVb	229 (7.1)
Presence of distant metastasis[‡]	
Yes	229 (7.1)
No	3,009 (92.9)
Distant metastatic location[‡,¶]	
Lymph node	39 (55.7)
Liver	20 (28.6)
Lung	14 (20.0)
Bone	14 (20.0)
Stomach	3 (4.3)
Others	6 (8.6)
Biomarkers	
PD-L1 positive[#]	20 (58.8)
EGFR positive**	12 (29.3)
HER2 positive[††]	8 (32.0)

EC, esophageal cancer; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death ligand 1; SD, standard deviation. *Data are *n* (%) unless otherwise stated. [†]Information on residential area was collected from patients' medical insurance records or medical record registration address. [‡]Percentages are based on non-missing data. [§]Classified according to derived rules for TNM staging. [¶]Analyzed on the basis of 95 patients (including 88 patients with M1 stage at initial diagnosis and 7 patients with unknown M stage at initial diagnosis and non-missing data on distant metastatic location or number of metastatic lesions). [#]Based on 34 patients with qualitative results. **Based on 41 patients with qualitative results. [††]Based on 25 patients with qualitative results.

Palliative therapy was administered to 50.7% of patients with unresectable early and locally advanced EC (**Table 4**). Chemotherapy was the most frequently used palliative treatment (27.8%), and the most common regimens were platinum-based doublet therapy: platinum + taxane (66.5%) and platinum + pyrimidines (16.1%). A minority of patients (4.8%) received a platinum-based triplet (platinum + taxane + pyrimidines).

Table 3 Initial treatment for patients with resectable EC

Treatment pattern*	Early-stage (*n* = 429)	Locally advanced (*n* = 1,713)	Total (*n* = 2,142)
Initial treatment pattern	*n* = 429	*n* = 1,713	*n* = 2,142
Radical surgery	420 (97.9)	1,569 (91.6)	1,989 (92.9)
Neoadjuvant therapy	9 (2.1)	144 (8.4)	153 (7.1)
Surgery type[†, ‡]	*n* = 420	*n* = 1,569	*n* = 1,989
Endoscopic resection	9 (2.1)	6 (0.4)	15 (0.8)
Minimally invasive esophagectomy	285 (67.9)	799 (51.1)	1,084 (54.6)
Open esophagectomy	126 (30.0)	760 (48.6)	886 (44.6)
Neoadjuvant treatment pattern[§]	*n* = 9	*n* = 144	*n* = 153
Chemotherapy	9 (100.0)	122 (84.7)	131 (85.6)
Chemotherapy alone	9 (100.0)	120 (83.3)	129 (84.3)
With targeted therapy	0	2 (1.4)	2 (1.3)
Radiotherapy	0	1 (0.7)	1 (0.7)
Chemoradiotherapy	0	21 (14.6)	21 (13.7)
Neoadjuvant chemotherapy regimen[§]	*n* = 9	*n* = 122	*n* = 131
Platinum + taxane	7 (77.8)	105 (86.1)	112 (85.5)
Platinum + pyrimidines	0	12 (9.8)	12 (9.2)
Platinum + taxane + pyrimidines	2 (22.2)	5 (4.1)	7 (5.3)
Neoadjuvant chemotherapy cycles[§]	*n* = 9	*n* = 122	*n* = 131
Median (range)	2.0 (1–3)	2.0 (1–4)	2.0 (1–4)

EC, esophageal cancer. *Data are *n* (%) unless otherwise stated. [†]Percentages are based on non-missing data. [‡]In patients receiving surgery as their initial treatment. [§]In patients receiving neoadjuvant therapy as their initial treatment.

Among the 229 patients with advanced-stage EC, 84.6% received systemic therapy as an initial treatment. The most common form of systemic therapy was chemotherapy (93.4%), primarily platinum-based doublet chemotherapy (**Table 5**). Patients received first-line systemic chemotherapy for a median of 46.0 (range 1–191) days and a median of 3.0 (range 1–9) cycles.

Subsequent treatment patterns in patients receiving surgery

Among all patients receiving adjuvant therapy after surgery (*n* = 503; including those also receiving neoadjuvant therapy), the most common treatment was chemotherapy (75.0%), predominantly platinum + taxane (59.6%) or platinum + pyrimidines (27.1%) (**Table 6**). For patients receiving adjuvant therapy after surgery alone, chemotherapy was the most common (74.8%) postoperative regimen, and was followed by chemoradiotherapy (17.3%), and radiotherapy (7.9%) (**Table 7**). Platinum + taxane was the most common chemotherapy and chemoradiotherapy regimen (58.5% and 34.2%, respectively). The median number of chemotherapy cycles was 3 (range 1–7), and the mean duration of treatment was 60.6 days. Among patients receiving adjuvant therapy after neoadjuvant therapy and surgery, the most common treatment was chemotherapy (76.6%), which was followed by chemoradiotherapy (14.9%), and radiotherapy (4.3%) (**Table 8**). Platinum + taxane was the most common chemotherapy and chemoradiotherapy regimen (69.4% and 71.4%, respectively). The median number of chemotherapy cycles was 2.0 (range 1–6), and the mean duration of treatment was 31.7 (26.5) days.

Subsequent treatment patterns in patients receiving systemic therapy

Among patients with advanced-stage disease receiving first-line systemic therapy (*n* = 197), 18 (9.1%) subsequently

Table 4 Initial treatment for patients with unresectable EC

Treatment pattern*	Early-stage (*n* = 43)	Locally advanced (*n* = 785)	Total (*n* = 828)
Initial treatment pattern	*n* = 43	*n* = 784	*n* = 827
Radical treatment	9 (20.9)	398 (50.8)	407 (49.2)
Radical chemoradiotherapy	4 (9.3)	258 (32.9)	262 (31.7)
Radical radiotherapy	5 (11.6)	140 (17.9)	145 (17.5)
Palliative treatment	34 (79.1)	386 (49.2)	420 (50.7)
Surgery	18 (41.9)	28 (3.6)	46 (5.6)
Chemotherapy	6 (14.0)	224 (28.6)	230 (27.8)
Radiotherapy	3 (7.0)	41 (5.2)	44 (5.3)
Chemoradiotherapy	7 (16.3)	93 (11.9)	100 (12.1)
Radical chemoradiotherapy regimen[†]	*n* = 4	*n* = 258	*n* = 262
Pyrimidines	1 (25.0)	81 (31.4)	82 (31.3)
Taxane	0	6 (2.3)	6 (2.3)
Platinum + taxane	1 (25.0)	132 (51.2)	133 (50.8)
Platinum + pyrimidines	1 (25.0)	26 (10.1)	27 (10.3)
Platinum + taxane + pyrimidines	1 (25.0)	3 (1.2)	4 (1.5)
Others	0	10 (3.9)	10 (3.8)
Total dose of radiation, Gy[†, ‡]	*n* = 4	*n* = 258	*n* = 262
Median (Q1, Q3)	115.20 (55.00, 172.20)	64.00 (60.00, 116.00)	64.00 (60.00, 116.00)
Radical chemoradiotherapy cycles[†]	*n* = 4	*n* = 258	*n* = 262
Median (range)	2.0 (1–4)	2.0 (1–9)	2.0 (1–9)
Palliative chemotherapy regimen[§]	*n* = 6	*n* = 224	*n* = 230
Platinum + taxane	1 (16.7)	152 (67.9)	153 (66.5)
Platinum + pyrimidines	5 (83.3)	32 (14.3)	37 (16.1)
Platinum + taxane + pyrimidines	0	11 (4.9)	11 (4.8)
Taxane	0	6 (2.7)	6 (2.6)
Taxane + pyrimidines	0	4 (1.8)	4 (1.7)
Irinotecan-based regimen	0	1 (0.4)	1 (0.4)
Others	0	18 (8.1)	18 (7.9)
Palliative chemotherapy cycles[§]	*n* = 6	*n* = 224	*n* = 230
Median (range)	1.0 (1–3)	2.0 (1–12)	2.0 (1–12)

EC, esophageal cancer; SD, standard deviation. *Data are *n* (%) unless otherwise stated, on the basis of patients with non-missing data. [†]In patients receiving radical chemoradiotherapy as their initial treatment. [‡]The total dose of radiation included the dose to primary and metastatic lesions. [§]In patients receiving palliative chemotherapy as their initial treatment.

received second-line therapy during the study follow-up period, typically further systemic therapy (77.8%), primarily chemotherapy (94.4%). Two patients (11.1%) also started third-line treatment with systemic therapy (chemotherapy, 50.0%), or combined radiotherapy plus systemic therapy (50.0%).

Table 5 Initial treatment for patients with advanced-stage EC (palliative treatment)

Treatment pattern*	Total (*n* = 229)
Initial treatment pattern	*n* = 228
Surgery[†]	12 (5.3)
Radiotherapy	23 (10.1)
Systemic therapy	193 (84.6)
With radiotherapy	74 (32.5)
First-line systemic therapy[†, ‡]	*n* = 197
Chemotherapy	184 (93.4)
Immunotherapy	1 (0.5)
Targeted therapy	1 (0.5)
Combined therapy	11 (5.6)
Chemotherapy + EGFR inhibitor	7 (3.6)
Chemotherapy + HER2 inhibitor	2 (1.0)
Chemotherapy + PD-1/PD-L1 inhibitor	1 (0.5)
Chemotherapy + VEGF/VEGFR inhibitor	1 (0.5)
Chemotherapy regimen[§]	*n* = 195
Pyrimidines	16 (8.2)
Taxane	2 (1.0)
Platinum + taxane	120 (61.5)
Platinum + pyrimidines	23 (11.8)
Platinum + taxane + pyrimidines	12 (6.2)
Others	17 (8.7)
Chemotherapy cycles	*n* = 195
Median (range)	3.0 (1–9)

EC, esophageal cancer; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor; PD-1/PD-L1, programmed death (ligand) 1; SD, VEGF(R), vascular endothelial growth factor (receptor). *Data are *n* (%) unless otherwise stated, on the basis of patients with non-missing data. [†]Four patients received systemic therapy after surgery and were also included in the results for first-line systemic therapy. [‡]In patients receiving systemic therapy as their initial treatment. [§]In patients receiving a chemotherapy regimen as their first-line systemic initial treatment.

Recurrence

Recurrence occurred in 19/2,549 (0.7%) patients with resectable or unresectable early-stage or locally advanced EC who received radical treatment within the 6 month observation period; most cases involved distant recurrence (17/19 cases) and typically affected the liver (6/17 cases). Progression was recorded in 8/197 (4.1%) patients with advanced-stage disease after first-line systemic therapy.

Discussion

The results of this national, multicenter retrospective study describe the clinicopathologic features and current treatment patterns for patients with EC in China, and is, to our knowledge, the largest dataset of EC characteristics and treatment patterns before the introduction of immunotherapy. These results can therefore serve as baseline data for exploring the effects of immunotherapy on patient outcomes, understanding unmet clinical needs, and providing new ideas for medical practice and research and development.

This study included a lower proportion of patients with stage IV EC (494/3,207, 15.4%) than a prior study describing the characteristics of EC in China (23%)[30]. This difference might be explained by several factors. First, only patients with EC without prior anti-tumor treatment were included; therefore, patients with recurrent metastases during the eligibility period were excluded from the present study. Patients with recurrent metastases will be included in the subsequent CHANNEL2 study, in which EC treatment patterns in the era of immunotherapy will be explored. Second, the recent promotion of early screening and diagnosis in China might have resulted in EC identification at earlier stages than in the prior study. Finally, because a high proportion of study sites were located in hospitals with strong surgical departments, a high proportion of newly diagnosed patients were seen in surgical departments. Because patients would be seen in such departments only if they had potentially resectable disease, i.e., early and locally advanced disease, the overall proportion of patients with stage IV EC included in this study might have been affected.

Our results indicated that neoadjuvant therapy for tumor downstaging before surgery was uncommon among patients with resectable EC. This finding probably reflects the large proportion of patients with early TNM stages (T0–T2), in whom surgeons were confident that direct R0 resection could be performed without a need for neoadjuvant therapy. In addition, neoadjuvant treatment is not usually considered a standard treatment approach for patients with early-stage resectable EC, because of limited evidence of an associated survival benefit[10]. When neoadjuvant therapy is warranted, the 2018 Chinese Society for Clinical Oncology (CSCO) guidelines for

Table 6 Adjuvant therapy in patients with resectable EC receiving surgery regardless of neoadjuvant therapy

Treatment pattern*	Early-stage (*n* = 34)	Locally advanced (*n* = 469)	Total (*n* = 503)
Adjuvant treatment	*n* = 34	*n* = 469	*n* = 503
Chemotherapy[†]	30 (88.2)	347 (74.0)	377 (75.0)
Radiotherapy	1 (2.9)	37 (7.9)	38 (7.6)
Chemoradiotherapy	3 (8.8)	83 (17.7)	86 (17.1)
Targeted therapy[‡]	0	2 (0.4)	2 (0.4)
Chemotherapy regimen	*n* = 30	*n* = 347	*n* = 377
Pyrimidines[§]	2 (6.7)	12 (3.5)	14 (3.7)
Platinum + taxane	12 (40.0)	212 (61.3)	224 (59.6)
Platinum + pyrimidines	15 (50.0)	87 (25.1)	102 (27.1)
Platinum + taxane + pyrimidines	1 (3.3)	26 (7.5)	27 (7.2)
Irinotecan-based regimen[‡]	0	1 (0.3)	1 (0.3)
Others	0	48 (13.9)	48 (12.8)

EC, esophageal cancer. *Data are *n* (%) unless otherwise stated, on the basis of patients with non-missing data. [†]One patient with locally advanced EC received chemotherapy combined with targeted therapy. [‡]Only after initial neoadjuvant therapy. [§]Only after initial surgery.

the diagnosis and treatment of EC recommend neoadjuvant concurrent chemoradiotherapy as a first-level expert recommendation, and neoadjuvant chemotherapy as a second-level expert recommendation for resectable locally advanced EC[5]. Accordingly, neoadjuvant concurrent chemoradiotherapy and neoadjuvant chemotherapy were the 2 most commonly used modalities among patients receiving neoadjuvant therapy in the present study. Therefore, exploring any changes in the use of preoperative neoadjuvant chemotherapy in patients diagnosed with EC after the introduction of immunotherapy will be of interest.

The proportion of patients receiving adjuvant therapy after surgery (22.9%) in the present study was slightly lower than that reported in prior studies by Luo et al.[26] in 2023 (including patients with an EC diagnosis from 2010–2019) and Mao et al.[31] in 2020 (including patients with an EC diagnosis from 2009–2014). However, this proportion is in line with findings from a nationwide database analysis in which 21.2% of patients undergoing surgery for EC received adjuvant chemotherapy (including patients with an EC diagnosis in 2015)[32]. This discrepancy might be explained by a lack of broad consensus regarding the benefits and use of adjuvant therapy when patients in those studies received treatment. In addition, current treatment guidelines recommend adjuvant chemotherapy for only selected patients, for example, those with pathologically confirmed regional lymph node metastasis[5,10].

Most patients in the present study received radical treatment. Most patients with resectable EC underwent radical surgery, primarily minimally invasive esophagectomy or open esophagectomy. Approximately half the patients with unresectable disease received initial radical therapy; although radical chemoradiotherapy (31.7%) was the most frequently used regimen, it might have been expected to have been used in a higher proportion of patients, given that definitive chemoradiotherapy-based integrated therapy is recommended as the first choice for patients with unresectable EC in the Chinese national treatment guidelines[5]. Toxicity concerns with definitive chemoradiotherapy[33,34], or discrepancies in access to radiotherapy resources across China[35], might potentially have limited the use of this regimen during the study period, before the publication of these guidelines in 2018. However, this result is generally consistent with that from a previous study in Korea (including patients from 2005–2017) reporting the use of definitive chemoradiotherapy in ~40% of patients with unresectable EC[36].

In our study, for patients with advanced EC, initial treatments consisted primarily of chemotherapy, most frequently platinum + taxane (61.5%), followed by platinum + pyrimidines (11.8%). Although no consensus exists regarding the optimal chemotherapy regimen for East Asian patients with advanced EC, current data appear to support both platinum + taxane and platinum + fluoropyrimidine regimens[24].

Table 7 Adjuvant therapy in patients with resectable EC receiving only surgery (no neoadjuvant therapy)

Treatment pattern*	Early-stage (*n* = 32)	Locally advanced (*n* = 424)	Total (*n* = 456)
Adjuvant treatment pattern	*n* = 32	*n* = 424	*n* = 456
Chemotherapy[†]	28 (87.5)	313 (73.8)	341 (74.8)
Radiotherapy	1 (3.1)	35 (8.3)	36 (7.9)
Chemoradiotherapy[‡]	3 (9.4)	76 (17.9)	79 (17.3)
Concurrent	2 (6.3)	49 (11.6)	51 (11.2)
Sequential	1 (3.1)	27 (6.4)	28 (6.1)
Adjuvant chemotherapy regimen	*n* = 28	*n* = 313	*n* = 341
Pyrimidines	2 (7.1)	12 (3.8)	14 (4.1)
Platinum + taxane	10 (35.7)	189 (60.6)	199 (58.5)
Platinum + pyrimidines	15 (53.6)	80 (25.6)	95 (27.9)
Platinum + taxane + pyrimidines	1 (3.6)	25 (8.0)	26 (7.6)
Others	0	6 (1.9)	6 (1.8)
Median chemotherapy cycles (range)	3.0 (1–5)	3.0 (1–7)	3.0 (1–7)
Mean duration of treatment, days (SD)	79.8 (50.5)	59.0 (44.9)	60.6 (45.6)
Adjuvant chemoradiotherapy regimen	*n* = 3	*n* = 76	*n* = 79
Pyrimidines	3 (100.0)	20 (26.3)	23 (29.1)
Platinum + taxane	0	27 (35.5)	27 (34.2)
Platinum + pyrimidines	0	16 (21.1)	16 (20.3)
Platinum + taxane + pyrimidines	0	4 (5.3)	4 (5.1)
Others	0	9 (11.8)	9 (11.4)
Median chemoradiotherapy cycles (range)	1.0 (1–2)	2.0 (1–5)	2.0 (1–5)
Mean duration of treatment, days (SD)	19.5 (26.2)	59.6 (40.8)	58.5 (40.9)
Type of radiotherapy	*n* = 1	*n* = 22	*n* = 23
3D-radiotherapy	0	1 (4.5)	1 (4.3)
Intensity-modulated radiotherapy	1 (100.0)	19 (86.4)	20 (87.0)
Others	0	2 (9.1)	2 (8.7)
Total dose of radiation, Gy[§]	*n* = 1	*n* = 35	*n* = 36
Median (Q1, Q3)	111.00 (111.00, 111.00)	50.00 (45.00, 50.40)	50.00 (45.00, 50.40)

EC, esophageal cancer; SD, standard deviation. *Data are *n* (%) unless otherwise stated, on the basis of patients with non-missing data. [†]One patient with locally advanced EC received chemotherapy combined with targeted therapy. [‡]One patient with locally advanced EC received chemoradiotherapy combined with targeted therapy. [§]The total dose of radiation included the dose to primary and metastatic lesions.

Taxane-based regimens are widely used in China as concurrent chemotherapy for patients with EC[34]. In addition, infusion of a taxane can be completed within 1 day, whereas pyrimidines require continuous infusion over 48 h. Because platinum + taxane might provide greater disease control and survival benefits than other regimens[37], as well as patient convenience and conservation of medical resources, our finding that platinum + taxane was most frequently used might reflect that this chemotherapy regimen was preferred for advanced EC in China during the study period. Only a small proportion

Table 8 Adjuvant therapy in patients with resectable EC receiving neoadjuvant therapy and surgery

Treatment pattern*	Early-stage (*n* = 2)	Locally advanced (*n* = 45)	Total (*n* = 47)
Adjuvant treatment pattern	*n* = 2	*n* = 45	*n* = 47
Chemotherapy[†]	2 (100.0)	34 (75.6)	36 (76.6)
Radiotherapy	0	2 (4.4)	2 (4.3)
Chemoradiotherapy	0	7 (15.6)	7 (14.9)
Concurrent	0	6 (13.3)	6 (12.8)
Sequential	0	1 (2.2)	1 (2.1)
Adjuvant chemotherapy regimen	*n* = 2	*n* = 34	*n* = 36
Platinum + taxane	2 (100.0)	23 (67.6)	25 (69.4)
Platinum + pyrimidines	0	7 (20.6)	7 (19.4)
Platinum + taxane + pyrimidines	0	1 (2.9)	1 (2.8)
Irinotecan-based regimen	0	1 (2.9)	1 (2.8)
Others	0	2 (5.9)	2 (5.6)
Median chemotherapy cycles (range)	1.0 (1–1)	2.0 (1–6)	2.0 (1–6)
Mean duration of treatment, days (SD)	1.5 (0.7)	33.7 (26.2)	31.7 (26.5)
Adjuvant chemoradiotherapy regimen		*n* = 7	
Pyrimidines	–	2 (28.6)	–
Platinum + taxane	–	5 (71.4)	–
Median chemoradiotherapy cycles (range)	–	2.0 (1–3)	–
Mean duration of treatment, days (SD)	–	25.0 (15.6)	–
Type of radiotherapy		*n* = 5	
Intensity-modulated radiotherapy	–	5 (100.0)	–
Total dose of radiation, Gy[‡]	–	*n* = 7	–
Median (Q1, Q3)		50.00 (50.00, 95.00)	

EC, esophageal cancer; SD, standard deviation. *Data are *n* (%) unless otherwise stated, on the basis of patients with non-missing data. [†]One locally advanced patient received chemotherapy combined with targeted therapy. [‡]The total dose of radiation included the dose to primary and metastatic lesions.

of patients initiated second- or third-line systemic therapy, possibly as a result of the short observation period; this finding might also be largely explained by the paucity of effective second-line therapeutic options for patients with advanced EC[38]. Indeed, the choice of second- and third-line regimens in the present study was heterogeneous, thereby reflecting a lack of definitive direction regarding which regimen should be used.

Traditional treatment methods have demonstrated limited survival benefits for patients with EC: single and combination chemotherapy regimens have shown a response duration of 4–6 months[14] and median overall survival of 5.5–9.5 months[39-42]. Consequently, an urgent need existed to develop new treatment methods to improve survival benefits with targeted agents and immunotherapy in this patient population. Immunotherapy has since become the standard treatment for advanced EC, while also providing an alternative option for patients with locally advanced disease[43]. Now that the clinicopathological characteristics and treatment patterns for Chinese patients with EC before the introduction of immunotherapy have been characterized, the ongoing CHANNEL2 study is aimed at describing subsequent treatment characteristics in the era of immunotherapy. That study will further indicate the value of immunotherapy for the real-world treatment of EC in China.

Limitations of this study include those inherent to the retrospective design, such as sample representativeness, primarily because of the inclusion of first-diagnosis inpatients, data completeness, and the implementation of specifications. In addition, the use of rule derivation for some of the missing data might have led to bias. A risk of selection bias also existed, because patients were generally selected from large cancer centers, thus potentially limiting the generalizability of the findings to the wider Chinese population. Finally, the relatively short follow-up period led to a short observation time window and limited the collection of data regarding subsequent treatment patterns. However, examining those patterns was not the main purpose of the present study.

In conclusion, in this large observational study of patients with advanced EC treated before the introduction of immunotherapy in China, most patients with early stage or locally advanced EC underwent initial surgery without preoperative treatment, and patients with advanced EC received initial chemotherapy, with platinum + taxane as the most common regimen. The subsequent CHANNEL2 study will explore the treatment patterns of Chinese patients with EC in the era of immunotherapy, and will enable assessment of any changes or differences with respect to the era of chemotherapy described herein. We believe that these findings will help identify unmet needs in clinical practice.

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Conflict of interest statement

Danfeng Shi, Jing Qian, Si Shi, and Fengshi Dong are employees of MSD China. Lin Shen received grants to their institution from BeiGene and participated in data safety monitoring boards or advisory boards for MSD China, Boehringer Ingelheim, Servier Pharmaceuticals, AstraZeneca, and Transcenta Holding. The other authors disclose no potential conflicts of interest.

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Data availability statement

The data generated in this study are available upon request from the corresponding authors.

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