original report abstract

Safety and Effectiveness of Chemotherapy for Metastatic Esophageal Cancer in a Community Hospital in Brazil

Carolina Ribeiro Victor, MD[1]; Fernanda Kaori Fujiki, MD[1]; Flavio Roberto Takeda, MD, PhD[1]; Paulo Marcelo Gehm Hoff, MD, PhD[1]; and Tiago Biachi de Castria, MD, PhD[1]

PURPOSE Despite epidemiologic and molecular differences between esophageal and stomach cancers, most published studies have included patients with either disease in a metastatic scenario. We evaluated the safety and effectiveness of chemotherapy in patients with metastatic esophageal cancer in the community setting.

PATIENTS AND METHODS We performed a retrospective cohort study of patients with synchronous metastatic esophageal cancer treated at a public hospital between 2008 and 2016. Patients were grouped according to a prescribed chemotherapy protocol: platinum and taxane (group A); platinum and irinotecan (group B); platinum and fluoropyrimidine (group C); and without platinum (group D).

RESULTS Of the 1,789 patients with esophageal cancer treated, we included 397 with metastatic disease at presentation. Squamous cell carcinoma was the most frequent histology (78.8%). Median overall survival (OS) was 7 months (95% CI, 6.15 to 7.85 months). Chemotherapy was administered to 285 patients, who reached a median OS of 9.0 months (95% CI, 8.0 to 9.9 months); for 112 patients who did not receive treatment, median OS was 3 months (95% CI, 2.3 to 3.7 months; $P < .001$). The most used combination was platinum plus irinotecan (A; 55.5%). Disease control with in groups A, B, C, and D was 39.2%, 30.1%, 53% and 14.3%, respectively. Patients in group C reached a median OS of 17 months (95% CI, 13.1 to 20.8 months; $P = .034$). No differences were observed in median OS obtained with other protocols (9 months). The toxicity profile was different according to chemotherapy, with more severe events (hematologic, diarrhea, and number of days hospitalized) occurring in group B.

CONCLUSION Platinum plus paclitaxel or platinum plus irinotecan provided similar OS in community patients, although patients receiving irinotecan experienced more severe events. In the adenocarcinoma population, a fluoropyrimidine plus platinum–based regimen, although less frequently used, had a more favorable toxicity profile, with superior median OS and disease control.

INTRODUCTION

Esophageal cancer is the eighth most common cancer worldwide and the sixth leading cause of cancer-related mortality. In 2018, approximately 440,000 new esophageal cancer cases and 370,000 deaths resulting from cancer were estimated to occur worldwide. More than 80% of all esophageal cancer cases were estimated to occur in developing countries.[1]

Two main histologic subtypes comprise 90% of esophageal cancer cases: esophageal adenocarcinoma (EAC), which commonly arises in the distal esophagus or esophagogastric junction (EGJ) and is rapidly increasing in incidence and has become the predominant type in Western countries[1,2], and esophageal squamous cell carcinoma (ESCC), which is related to a pathology of the cervical and upper and thoracic esophagus and remains the predominant type in Asia, Africa, and South America.[1]

In Latin America, the highest incidence rates of esophageal cancer have been observed in the Southern Cone of South America (Brazil, Uruguay, Argentina, and Chile), and ESCC is the predominant histologic subtype (approximately 70%).[2] Although in some of these countries, populations have the habit of drinking maté tea at a high temperature, which is related to development of esophageal cancer,[3] the high incidence of ESCC is also attributable to smoking and alcohol use.[2] A multicenter case-control study conducted in this region revealed that simultaneous use of tobacco and alcohol increased the risk of ESCC by eight-fold.[4]

In Brazil, esophageal cancer represents the sixth highest mortality cause, and more than half of diagnosed cases

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on June 11, 2019 and published at ascopubs.org/journal/jgo on July 31, 2019: DOI https://doi.org/10.1200/JGO.19.00103

CONTEXT

Key Objective

There is no standard treatment of metastatic esophageal disease; is it safe and effective to administer chemotherapy regimens used in clinical practice in a large community hospital?

Knowledge Generated

In our cohort, platinum doublets with paclitaxel, irinotecan, or fluoropyrimidine were equally effective (disease control and median overall survival). However, they presented different profiles of treatment-related adverse events, with more severe events (hematologic events, diarrhea, and number of days hospitalized) occurring in patients receiving platinum plus irinotecan. In the adenocarcinoma population, a fluoropyrimidine and platinum–based regimen, although less frequently used in our study, had a more favorable toxicity profile, with superior median overall survival and disease control.

Relevance

In institutions with a limited budget, without access to infusion pumps, platinum and paclitaxel should be an option, with fewer adverse effects than platinum and irinotecan, especially in squamous carcinoma histology.

are unresectable or metastatic,[2] with a 5-year survival rate lower than 3%.[2] A retrospective analysis conducted between 2009 and 2012 at our institution included 565 patients (ESCC, n = 444; EAC, n = 105). Only 20% of patients with ESCC and 30% of those with EAC were eligible for curative-intent treatment.[5]

Palliative chemotherapy is a treatment widely accepted for metastatic esophageal carcinoma (MEC), but until recently, the evidence of an overall survival (OS) benefit was controversial.[6] Eleven randomized trials of palliative chemotherapy or targeted agent versus best support of care for MEC and EGJ tumors were included in a Cochrane meta-analysis published in 2017.[7] The authors demonstrated an increase of less than 1 month in OS favoring the treatment arm, with a hazard ratio of 0.81 (95% CI, 0.71 to 0.92), and improvement in quality of life, despite a higher incidence of grade 3 or worse treatment-associated toxicities in patients who received treatment. Nevertheless, several published studies have included patients with either histologic subtype of MEC as well as patients with metastatic gastric cancer (mainly adenocarcinoma) in the same trial, which makes it difficult to analyze results regarding primary tumor site and histology, limiting external validation.

Long-term remission may occasionally be achieved with chemotherapy; however, there is no standard treatment protocol, and different regimens of chemotherapy are currently used worldwide.[8] Several institutions have adopted regimens that do not require either portable pumps or implantable access devices; in general, a platinum-based doublet, such as irinotecan plus cisplatin,[9] carboplatin plus paclitaxel,[10] or even cisplatin plus fluoropyrimidine,[11] has been used. The aim of our study was to analyze the effectiveness and safety of several combinations of chemotherapy agents in patients with MEC treated in a large community hospital.

PATIENTS AND METHODS

We performed a retrospective unicentric cohort study with data collected from medical records from consecutive patients from Instituto do Cancer do Estado de São Paulo, a public hospital that provides tertiary health care service, based in São Paulo, Brazil. All patients diagnosed with synchronous MEC (EAC or ESCC) from January 2008 to November 2016 were eligible. Patients were excluded if they had any of the following: local or locoregional disease, suitable for resection or chemoradiotherapy with curative intent; synchronous second malignancy, except nonmelanoma skin cancer; previous cancer within 5 years, except nonmelanoma skin cancer; receipt of any treatment at another institution, either with curative or palliative intent; or gastric or EGJ tumor.

Regarding treatment, we grouped patients who had received palliative chemotherapy into four groups according to chemotherapy regimen: platinum (cisplatin or carboplatin) plus paclitaxel (group A); platinum (cisplatin or carboplatin) plus irinotecan (group B); platinum (oxaliplatin or cisplatin) plus fluoropyrimidine (fluorouracil or capecitabine; group C); and chemotherapy without a platinum agent (once-per-week paclitaxel or fluorouracil; group D).

The primary objective was safety, determined by incidence of grade 3 or worse toxicity events, of chemotherapy regimens in community patients with MEC. The secondary objective was to evaluate radiologic response and effectiveness, determined by OS.

For all patients, the following characteristics were analyzed: age at the time of diagnosis (defined as age at the time of tumor biopsy), sex, histology, weight, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) at the first medical appointment at our hospital. Tumor staging was defined according to the American Joint Committee on Cancer criteria (seventh edition, 2010).[12] We also evaluated type of chemotherapy, start date, number of cycles, and incidence of any grade 3 or worse toxicities, categorized according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Fisher's exact test was used to compare absolute and relative frequencies. For continuous variables, measures of dispersion, variability (range and standard deviation), and measures of central tendency (mean and median) were calculated. Time-to-event variables were estimated using the Kaplan-Meier method. All analyses were performed using MedCalc (version 11.5.1.0; MedCalc, Mariakerk, Belgium), SPSS (version 18; SPSS, Chicago, IL), or STATA software (version 13.0; STATA, College Station, TX). The study was approved by the local ethics research committee (NP 1030/16).

RESULTS

A total of 1,745 patients with esophageal cancer were identified in our institution between January 2008 and November 2016; 397 patients with synchronous MEC were included according to inclusion and exclusion criteria (Fig 1A). Median age was 60 years (range, 25 to 95 years), and most patients were men and had PS (categorized by the ECOG scale) of 0, 1, or 2. Use of tobacco or alcohol (whether previous or current) was reported in 83.1% and 74.8% of patients, respectively. Median body mass index was 19.2 kg/m^2 (range, 11.5 to 47.6 kg/m^2). The most frequent histology was ESCC (78.8%), as summarized in Table 1. Chemotherapy regimens received by patients with different tumor histologies are shown in Figure 1B.

Among all patients, median ECOG PS was 2, with median OS of 7.0 months (95% CI, 6.15 to 7.85 months), as shown in Figure 2. In the 285 patients who received chemotherapy, median OS reached 9.0 months (95% CI, 8.03 to 9.96 months), whereas in patients who did not receive chemotherapy (n = 112; 28.2%), median OS was 3.0 months (95% CI, 2.30 to 3.69 months; $P < .001$).

Safety

Incidence of grade 3 to 5 treatment-related adverse events among all patients who received first-line chemotherapy was 42%. The toxicity profile was different according to chemotherapy regimen (Table 2); however, any grade 3 or worse toxicity event occurred in 55% of patients who received platinum plus irinotecan (group B), 37% of patients

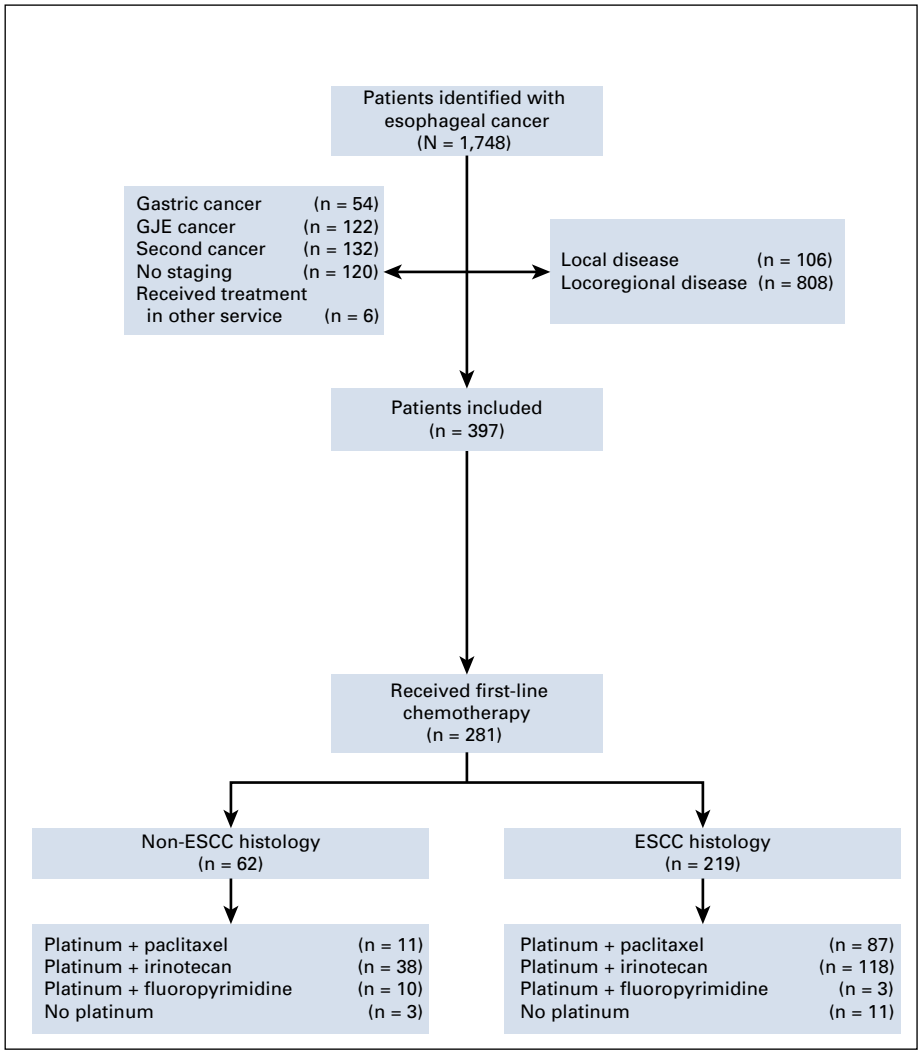

FIG 1. CONSORT diagram.

TABLE 1. Demographic and Clinical Characteristics of All Patients at Baseline (N = 397)

Characteristic	No. (%)
Age, years	
Median (range)	60 (25-95)
Male sex	328 (82.7)
BMI, kg/m^2	
Median (range)	19.2 (11.5-47.6)
Alcohol consumption	
Current and former	297 (74.8)
Tobacco use	
Never-smoker	50 (12.6)
Current and former smoker	330 (83.1)
Histologic type	
EAC	58 (14.6)
ESCC	313 (78.8)
Undifferentiated	22 (5.5)
Neuroendocrine tumor	4 (1.0)
ECOG PS (before chemotherapy)	
0	35 (8.8)
1	138 (34.8)
2	98 (24.8)
3	82 (20.7)
4	42 (10.8)
Most common sites of metastasis	
Lymph node	251 (63.2)
Lung	156 (39.3)
Liver	132 (33.2)
Bone	86 (21.7)
First-line treatment	281 (71.8)
Second-line treatment	117 (29.4)

Abbreviations: BMI, body mass index; EAC, esophageal adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; PS, performance status.

treated with platinum plus paclitaxel (group A), 38% of patients treated without a platinum compound (group D), and 21% of patients treated with platinum plus fluoropyrimidine (group C; $\chi^2 = 10.78$; $P = .013$).

Grade 3 to 5 hematologic toxicities occurred to 19.4% in patients treated with platinum plus paclitaxel (group A), 29.7% of those treated with platinum plus irinotecan (group B), 7.7% of those who received platinum plus fluoropyrimidine (group C), and 14.3% of those treated without a platinum compound (group D). Grade 3 or worse anemia occurred in 29.6% of patients in group B, 10.2% in group A, 15.3% in group D, and 7.14% in group C ($\chi^2 = 20.6$; $P = .014$). Patients treated with platinum plus irinotecan received more RBC transfusions per cycle compared with patients in others groups (0.3 *v* 0.04, 0.08, and zero transfusions per cycle in groups B, C, and D, respectively).

Grade 3 to 5 GI toxicities occurred in 5.1% of patients in group A, 12.2% in group B, and none in group C or D. Median weight loss during first-line chemotherapy was 2.3 kg, with no difference among the groups ($P = .7$). In groups A and B, 18.8% and 15.4% of patients, respectively, experienced infection and required inpatient antibiotic therapy, compared with 7.7% of patients in group C and 14.3% in group D.

In our cohort, there were 12 deaths related to chemotherapy treatment: one patient died as a result of diarrhea leading to acute renal failure, and 11 patients died as a result of infection up to 30 days after chemotherapy treatment (septic shock after pneumonia, n = 8; endocarditis, n = 1; brain abscess, n = 1; urinary tract infection by candida, n = 1; and septic shock after abdominal infection, n = 1). Incidence of all other toxicities was not significantly different among the groups (Table 2).

The total number of chemotherapy cycles delivered to patients in group A was 132; it was 577 cycles in group B, 47 in group C, and 31 in group D. Considering hospital admissions during and up to 30 days after end of first-line chemotherapy, the ratio of days of hospitalization to number of cycles in group B was 1.93 days per cycle; it was 0.36 in group A, 0.02 in group D, and zero in group C.

Chemotherapy Effectiveness

Platinum plus paclitaxel (group A). Ninety-eight patients were treated with platinum plus paclitaxel, representing 34.9% of the population; 11 patients had non-ESCC, and 87 had ESCC; 36.7% of patients had metastases in the lymph nodes only. Median OS was 9 months (95% CI, 7.3 to 10.6 months), and 29% of patients achieved partial or complete response as best response, 9.3% had stable disease, and 16.3% experienced disease progression (Table 3; Fig 3).

Platinum plus irinotecan (group B). Platinum plus irinotecan was administered to 156 patients (55.5%); 24.4% had metastases in the lymph nodes only; 38 patients had non-ESCC, and 118 had ESCC. In this population, median OS was 9 months (95% CI, 7.6 to 10.3 months), and complete or partial response was achieved in 21.8% of patients; 8.3% had stable disease, and 31.4% had progressive disease.

Platinum plus fluoropyrimidine (group C). Thirteen patients received platinum combined with fluoropyrimidine (4.6%); 10 patients had non-ESCC, and three patients had ESCC; only three patients had metastases exclusively in the lymph nodes. Median OS was 17 months (95% CI, 13.1 to 20.8 months; $P = .034$). Complete or partial response was reached in 46.2% of patients; 7.7% had stable disease, and 30.8% had progressive disease.

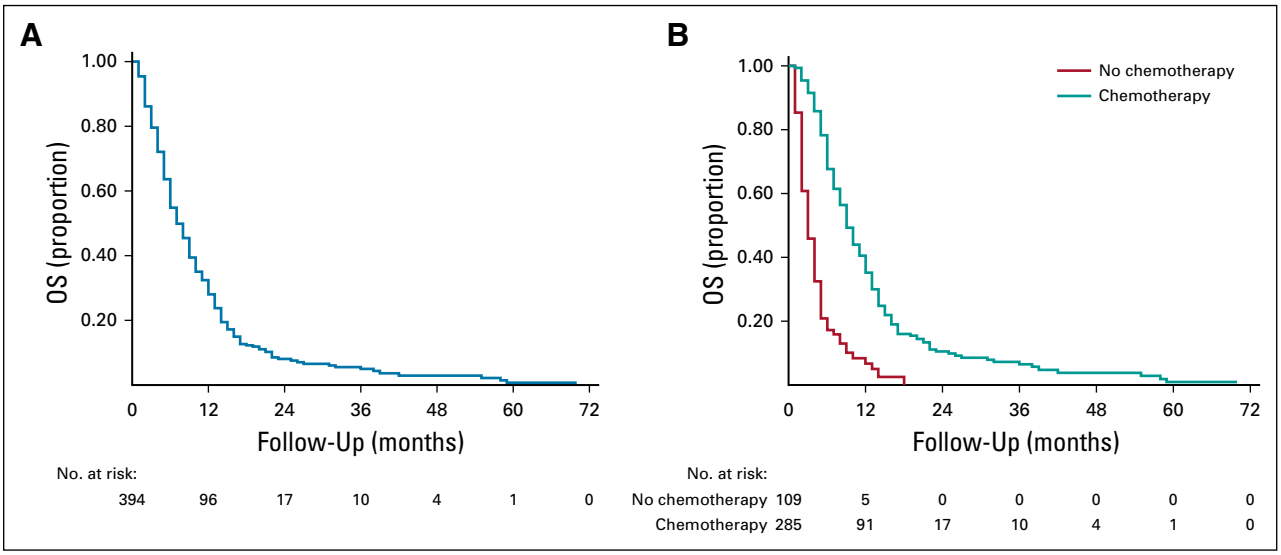

FIG 2. Kaplan-Meier curves of overall survival (OS) for (A) all patients and (B) by chemotherapy receipt.

Without platinum (group D). Five percent of patients underwent chemotherapy without a platinum compound (n = 14); three patients had non-ESCC, and 11 had ESCC; eight patients had metastases in the lymph nodes only. Ten patients received once-per-week paclitaxel, and four received once-per-week fluorouracil. Median OS was 9 months (95% CI, 2.9 to 15.0 months). Complete or partial response was achieved in 14.3% of patients, and 35.7% had progressive disease; no patients in this group had stable disease.

Histology

The most frequent histologic type was ESCC. In this subgroup, there was no difference among chemotherapy regimens (Table 4; Fig 4). However, in the subgroup of patients with EAC, there was a discrepancy in median OS according to chemotherapy scheme, ranging from 5 months with regimens without a platinum compound to 15 months with the platinum plus fluoropyrimidine regimen.

DISCUSSION

To our knowledge, this study is the first report of palliative chemotherapy results in esophageal carcinoma in Brazil with an expressive number of patients. Unfortunately, in most cases, such patients attend their first medical appointment with a high tumor burden, and consequently, they are already frail and malnourished, and have severe health conditions. In addition to potential benefits and harms of treatment, patient PS and comorbidities are considered in the decision of whether to offer systemic therapy or best support care alone.

In our cohort of community patients, more than 80% of patients were former or current smokers, and 75% reported alcohol consumption. There were fewer cases of obesity; patients had a median body mass index of 19 kg/m^2. It was not surprising that 80% of patients had ESCC. Therefore, our population was different from those of North America and Europe, where most studies have been performed, illustrating the importance of evaluating adverse effects and effectiveness in this population.

TABLE 2. Treatment-Related Adverse Events

	Group A: Platinum + Paclitaxel, %		Group B: Platinum + Irinotecan, %		Group C: Platinum + Fluoropyrimidine, %		Group D: Without Platinum, %	
Adverse Events	**Grade 3**	**Grades 4-5**	**Grade 3**	**Grades 4-5**	**Grade 3**	**Grades 4-5**	**Grade 3**	**Grades 4-5**
All	22.4	14.3	32	12.8	15.4	0	28.6	0
Anemia	11.2	1	20	1.3	0	0	14.3	0
Neutropenia	8.2	2	12.9	3.2	7.7	7.7/0	0	0
Thrombocytopenia	2	0	1.3	0	0	0	0	0
Vomiting	2	1	2.8	0	0	0	0	0
Diarrhea	2	3.1	9.8	2.8	0	0	0	0
Infection	13.3	5.1/4.1	10.3	3.8/1.3	7.7	0/0	14.3	0/0
Death within 30 days, No. (%)	4 (4.0)		8 (5.13)		0		0	

TABLE 3. First-Line Chemotherapy Schemes and Effectiveness

Outcomes	Group A: Platinum + Paclitaxel	Group B: Platinum + Irinotecan	Group C: Platinum + Fluoropyrimidine	Group D: Without Platinum
Use, No. (%)	98 (34.9)	156 (55.5)	13 (4.6)	14 (5.0)
Metastases in lymph nodes only, No. (%)	36 (36.7)	38 (24.4)	3 (23.0)	8 (57.1)
Best response, %				
CR/PR	29	21.8	46.2	14.3
SD	9.3	8.3	7.7	0
PD	18.6	31.4	30.8	35.7
No information	42.3	38.5	15.4	50
Median OS, months	9	9	17	9
95% CI	7.3 to 10.6	7.6 to 10.6	13.1 to 20.8	2.9 to 15

Abbreviations: CR, complete response; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

In our cohort, 55.5% of patients received cisplatin plus irinotecan as first-line chemotherapy. This regimen was adopted at our institution based on the phase II trial by Ilson et al.[9] In that study, the authors found a response rate of 57% and OS of 14 months, with the same activity in both EAC and ESCC. The regimen was also well tolerated, with acceptable myelosuppression, and patients who achieved a response experienced improved quality of life. Furthermore, in the Cancer and Leukemia Group B (CALGB) 80403 phase II trial (ClinicalTrials.gov identifier: NCT00381706), cisplatin plus irinotecan, despite being numerically inferior, had statistically similar efficacy—however was compared with FOLFOX (infusional fluorouracil, leucovorin, and oxaliplatin) or cisplatin plus infusional fluorouracil.[13]

Instituto do Cancer do Estado de São Paulo is part of the public health system in Brazil, a universal system with limited financial resources provided by the nation and individual states that guarantees free comprehensive health care to every individual in need. To optimize those resources, cisplatin plus irinotecan is widely used to avoid the need for implanted catheters for infusional fluorouracil. In addition, a vast majority of patients with MEC have ESCC and present with variable degrees of dysphagia, preventing the use of capecitabine.

Although several randomized clinical trials have been published in this field, heterogeneity exists across histologic subtype (biologic and response differences between ESCC and EAC) and anatomic position (gastric *v* esophageal). In general, a response rate of 30% to 45% and OS of 9 to 10 month have been achieved (Table 5) in other published trials.

In 2017, The Cancer Genome Atlas forum reported a genomic characterization of esophageal carcinoma[21] that showed subclasses of ESCC and demonstrated that EAC resembled

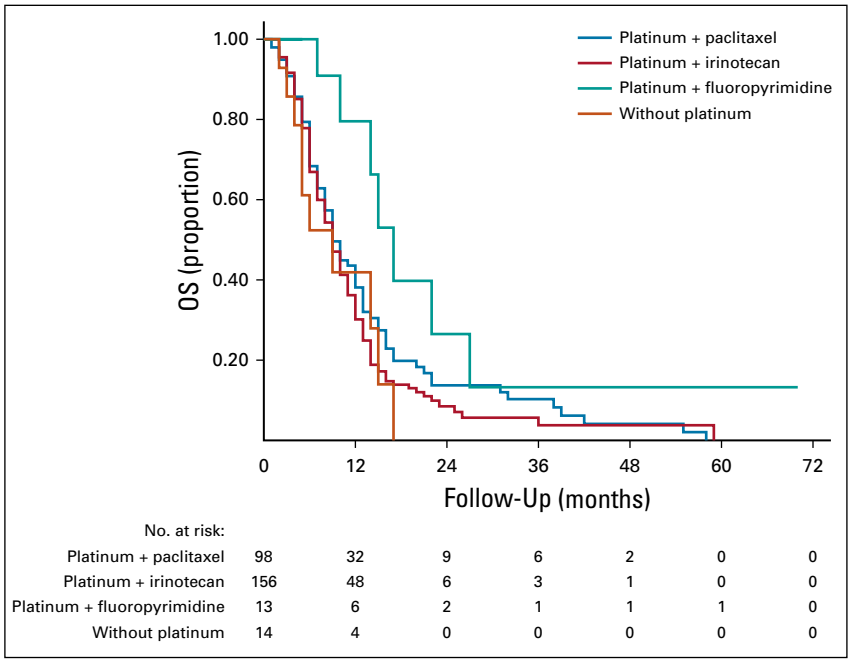

FIG 3. Kaplan-Meier curve of overall survival (OS) by treatment regimen received.

TABLE 4. Histologic Types According to Chemotherapy Schemes

	Median OS (95% CI; months)			
Histology	Group A: Platinum + Paclitaxel	Group B: Platinum + Irinotecan	Group C: Platinum + Fluoropyrimidine	Group D: Without Platinum
ESCC	10 (7.8 to 12.1)	9 (7.3 to 10.6)	10	9 (1.9 to 16)
EAC	12 (3.8 to 20.2)	12 (9.7 to 14.3)	15 (13.4 to 16.6)	5 (0.2 to 9.8)

Abbreviations: EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; OS, overall survival.

chromosomal instability subtype of gastric adenocarcinoma,[22] which is one of four major genomic subtypes: Epstein-Barr virus–positive tumors, microsatellite-unstable tumors, genomically stable tumors, and tumors with chromosomal instability. That study suggested a graduated molecular subclasses of gastroesophageal carcinoma.

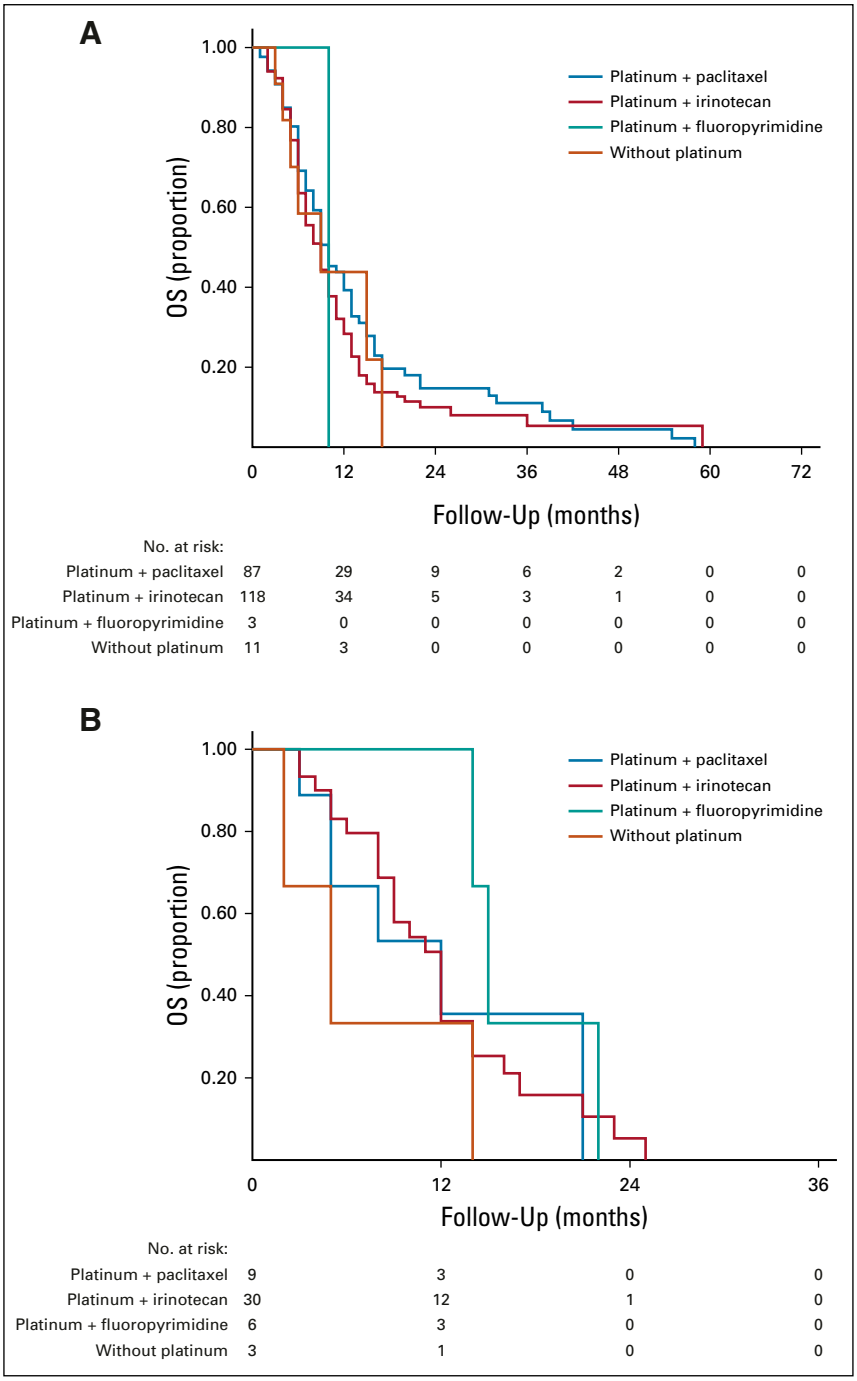

FIG 4. Kaplan-Meier curves of overall survival (OS) by treatment regimen received for patients with (A) esophageal squamous cell carcinoma and (B) esophageal adenocarcinoma.

TABLE 5. Combination Chemotherapy in Advanced Disease

Agent and Trial	No. of Patients	Response Rate, %	Median Survival (months)	EAC, %	ESCC, %
Cisplatin + fluorouracil					
Bleiberg[14]	88	40	8.2	0	100
Cisplatin + gemcitabine					
Urba[15]	64		7.3	81	16
Cisplatin + paclitaxel					
Ilson[16]	38	44	6.9	92	8
Liu[17]	398	42.5	13.4	0	100
Cisplatin + irinotecan					
Kim[18]	27	30	8.8	0	100
Ilson[9]	35	57	14.6	66	34
Cisplatin, fluorouracil, and paclitaxel					
Ilson[19]	61	48	10.8	51	49
Carboplatin + paclitaxel					
El-Rayes[20]	35	39	9	62	38
Cancer Genome Atlas Research Network[21]	134	39	15.5	75	25

Abbreviations: EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma.

Despite scarce evidence, guidelines from the European Society for Medical Oncology[23] state that advanced EAC is managed mostly according to the recommendations for gastric cancer.[24,25] However, the value of palliative chemotherapy is not clear in metastatic ESCC.

The main objective of our study was to assess the safety and effectiveness of drug combinations in community patients with esophageal cancer, excluding those with gastric or EGJ cancer. Moreover, we only analyzed synchronous MEC to avoid bias regarding the impact of previous treatment of local disease.

There are some limitations to our study. It was a single-center, retrospective, uncontrolled study. We had to rely on the reporting of adverse events in medical records, and our population already had poor PS at the first medical appointment (30% with ECOG PS of 3 or 4), probably because of the long time between the beginning of symptoms and diagnosis and consequently the initiation of treatment. Also, the four groups of chemotherapy regimens (groups A, B, C, and D) were created empirically to simplify comparisons, which could have created bias.

Because the literature on systemic treatment for metastatic ESCC is scarce,[9] our study is even more relevant, demonstrating that in community patients, platinum doublets with paclitaxel, irinotecan, or fluoropyrimidine are equally effective, with different toxicity profiles. In patients with EAC, a platinum doublet with fluoropyrimidine was superior to paclitaxel- or irinotecan-based chemotherapy, and combinations without a platinum agent were inferior to other schemes.

In our study, only 13 patients received platinum plus fluoropyrimidine because of preference for capecitabine (especially to avoid portable pumps or implantable access devices). This doublet (group C) was superior to treatments received by other groups, even with a small number of patients. However, caution is required; there is a risk of selection bias, because this population could have had better PS and lower tumor burden with less dysphagia.

Although superior effectiveness of the platinum plus fluoropyrimidine regimen is suggested, this finding may have resulted from selection bias. However, although platinum plus paclitaxel and platinum plus irinotecan had similar effectiveness, number of days hospitalized and frequency of severe toxicities (grade ≥ 3) were higher in patients who received platinum plus irinotecan (group B) compared with those who received platinum plus a taxane (group A), which suggests that taxane-based combinations may be evaluated in prospective studies, especially in cases of squamous carcinoma histology, similar to treatments offered in other primaries, such as anal canal and cervical cancers.[26,27]

In conclusion, platinum plus paclitaxel and platinum plus irinotecan provide similar disease control and median OS in MEC, mainly in ESCC. However, they presented different treatment-related adverse events (with more hematologic and diarrhea events in patients receiving irinotecan). In the EAC population, the fluoropyrimidine and platinum–based regimen, although less frequently used in our study, revealed a more favorable toxicity profile, with superior median OS and disease control. Patients with advanced disease should be encouraged to participate in clinical trials exploring novel strategies and chemotherapy combinations.

AFFILIATIONS

[1]Universidade de São Paulo Instituto do Cancer do Estado de São Paulo, São Paulo, Brazil
[2]Oncologia D'or, São Paulo, Brazil
[3]Centro de Oncologia, Hospital Sírio-Libanês, São Paulo, Brazil

CORRESPONDING AUTHOR

Carolina Ribeiro Victor, MD, Instituto do Câncer do Estado de São Paulo, Av. Dr. Arnaldo, 251, São Paulo, Brazil, 01246-000; e-mail: carolinarvictor@gmail.com.

AUTHOR CONTRIBUTIONS

Conception and design: Carolina Ribeiro Victor, Paulo Marcelo Gehm Hoff, Tiago Biachi de Castria
Administrative support: Carolina Ribeiro Victor, Flavio Roberto Takeda
Provision of study material or patients: Paulo Marcelo Gehm Hoff
Collection and assembly of data: Carolina Ribeiro Victor, Fernanda Kaori Fujiki, Tiago Biachi de Castria
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jgo/site/misc/authors.html.

Paulo Marcelo Gehm Hoff
Consulting or Advisory Role: United Health Group (I), Genzyme (I)
Research Funding: Bayer HealthCare Pharmaceuticals (Inst), Eisai (Inst), MSD Oncology (Inst), Novartis (Inst), Exelixis (Inst), Roche/Genentech (Inst), AstraZeneca/MedImmune (Inst)

Tiago Biachi De Castria
Speakers' Bureau: Roche
Travel, Accommodations, Expenses: Roche, Ipsen

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

We thank patients and their families, our colleagues from Instituto do Câncer do Estado de São Paulo, and the reviewers for their insights and comments on earlier versions of the manuscript.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018
2. Barrios E, Sierra MS, Musetti C, et al: The burden of oesophageal cancer in Central and South America. Cancer Epidemiol 44:S53-S61, 2016 (suppl 1)
3. Lubin JH, De Stefani E, Abnet CC, et al: Maté drinking and esophageal squamous cell carcinoma in South America: Pooled results from two large multicenter case-control studies. Cancer Epidemiol Biomarkers Prev 23:107-116, 2014
4. Castellsagué X, Muñoz N, De Stefani E, et al: Independent and joint effects of tobacco smoking and alcohol drinking on the risk of esophageal cancer in men and women. Int J Cancer 82:657-664, 1999
5. Tustumi F, Kimura CM, Takeda FR, et al: Prognostic factors and survival analysis in esophageal carcinoma [article in English and Portuguese]. Arq Bras Cir Dig 29:138-141, 2016
6. Adenis A, Penel N, Horn S, et al: Palliative chemotherapy does not improve survival in metastatic esophageal cancer. Oncology 79:46-54, 2010
7. Janmaat VT, Steyerberg EW, van der Gaast A, et al: Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer. Cochrane Database Syst Rev 11:CD004063, 2017
8. Cohen DJ, Leichman L: Controversies in the treatment of local and locally advanced gastric and esophageal cancers. J Clin Oncol 33:1754-1759, 2015
9. Ilson DH, Saltz L, Enzinger P, et al: Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol 17:3270-3275, 1999
10. Prithviraj GK, Baksh K, Fulp W, et al: Carboplatin and paclitaxel as first-line treatment of unresectable or metastatic esophageal or gastric cancer. Dis Esophagus 28:782-787, 2015
11. Hiramoto S, Kato K, Shoji H, et al: A retrospective analysis of 5-fluorouracil plus cisplatin as first-line chemotherapy in the recent treatment strategy for patients with metastatic or recurrent esophageal squamous cell carcinoma. Int J Clin Oncol 23:466-472, 2018
12. Edge SB, Compton CC: The American Joint Committee on Cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17:1471-1474, 2010
13. Enzinger PC, Burtness BA, Niedzwiecki D, et al: CALGB 80403 (Alliance)/E1206: A randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. J Clin Oncol 34:2736-2742, 2016
14. Bleiberg H, Conroy T, Paillot B, et al: Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer 33:1216-1220, 1997
15. Urba SG, Chansky K, VanVeldhuizen PJ, et al: Gemcitabine and cisplatin for patients with metastatic or recurrent esophageal carcinoma: A Southwest Oncology Group study. Invest New Drugs 22:91-97, 2004
16. Ilson DH, Forastiere A, Arquette M, et al: A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. Cancer J 6:316-323, 2000
17. Liu Y, Ren Z, Yuan L, et al: Paclitaxel plus cisplatin vs. 5-fluorouracil plus cisplatin as first-line treatment for patients with advanced squamous cell esophageal cancer. Am J Cancer Res 6:2345-2350, 2016
18. Kim M, Keam B, Kim TM, et al: Phase II study of irinotecan and cisplatin combination chemotherapy in metastatic, unresectable esophageal cancer. Cancer Res Treat 49:416-422, 2017
19. Ilson DH, Ajani J, Bhalla K, et al: Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 16:1826-1834, 1998
20. El-Rayes BF, Shields A, Zalupski M, et al: A phase II study of carboplatin and paclitaxel in esophageal cancer. Ann Oncol 15:960-965, 2004
21. Cancer Genome Atlas Research Network, Analysis Working Group: Asan University, BC Cancer Agency, et al: Integrated genomic characterization of oesophageal carcinoma. Nature 541:169-175, 2017

22. Cancer Genome Atlas Research Network: Comprehensive molecular characterization of gastric adenocarcinoma. Nature 513:202-209, 2014
23. Lordick F, Mariette C, Haustermans K, et al: Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 27:v50-v57, 2016 (suppl 5)
24. Bang YJ, Van Cutsem E, Feyereislova A, et al: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 376:687-697, 2010
25. Smyth EC, Verheij M, Allum W, et al: Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 27:v38-v49, 2016 (suppl 5)
26. Rao S, Sclafani F, Eng C, et al: InterAACT: A multicentre open label randomised phase II advanced anal cancer trial of cisplatin (CDDP) plus 5-fluorouracil (5-FU) vs carboplatin (C) plus weekly paclitaxel (P) in patients (pts) with inoperable locally recurrent (ILR) or metastatic treatment naïve disease—An International Rare Cancers Initiative (IRCI) trial. Ann Oncol 29, 2018 (abstr LBA21)
27. Kitagawa R, Katsumata N, Shibata T, et al: Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: The open-label randomized phase III trial JCOG0505. J Clin Oncol 33:2129-2135, 2015

