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Experience in Locally Advanced Esophageal Cancer with Definitive Chemoradiotherapy at the National Oncology Institute in the Period 2012-2022

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Abstract: *Introduction:* The World Health Organization (WHO) estimates 18 million people were diagnosed with cancers in 2020, of these 600,000 were esophageal cancer and ranks 6th in mortality. In Panama, in 2020, 58 new cases were diagnosed, with a lethality of 90%. Despite advances in the therapeutic approach and survival of localized esophageal cancer, we are unaware of the survival results associated with concomitant chemoradiotherapy treatment. *Methodology:* We conducted a retrospective study, reviewing the electronic medical records of patients with locally advanced esophageal cancer treated with Chemotherapy-Radiotherapy at the National Institute of Oncology from 2012 to 2022. Results were evaluated using the Kaplan Meier method, long rank test and a multivariate analysis with Cox regression. *Objective:* to evaluate the survival results in patient with locally advanced esophageal cancer treated with chemotherapy-radiotherapy. *Results:* 94 patients were evaluated, with a mean age of 64 years. The median time to progression (TPP) was 6 months and the median overall survival (OS) was 9 months. 69% patient has Eastern Cooperative Oncology Group (ECOG) 1, with a predominance of squamous histology in 89% and the degree of differentiation moderately differentiated in 55.3%. The main chemotherapy treatment was based on a scheme of weekly Carboplatin plus Paclitaxel in 41.5%, of which 66% received a dose of radiotherapy ≥45 Gy, with a 5-week extension time. A post-treatment radiographic response was evidenced with a clinical benefit of 36.2% and an objective response of 27.7%. The main adverse effects were dysphagia (16%), neutropenia (8.3%), nausea and vomiting (7.4%), and weight loss (7.4%). When analyzing the associated factors in relation to OS, in the multivariate analysis, the ECOG and the well-differentiated histological grade turned out to be significant association factors for better OS; but for the TTP, there were no associated factors identified when performing multivariate analysis. *Conclusions:* In this retrospective analysis, we found a median TTP of 6 months and a median OS of 9 months, which is below the values in the literature. The ECOG and the degree of differentiation were the factors associated with a better overall survival. Hematological and gastrointestinal adverse events were the most reported. It is important to choose patients in the best clinical condition for concomitant treatment with CT/RT to achieve better clinical results.

Keywords: Esophageal Cancer, Chemoradiotherapy, Overall Survival, Time to Progression

1. Introduction

According to the World Health Organization (WHO), of the slightly more than 18 million cancers diagnosed in 2020, more than 600,000 of these cases were esophageal cancer, representing 3.3% and being in the 7th position, along with cervical cancer, and was the 6th cancer that caused the most deaths that same year with 5.5%, more than half a million deaths [1]. In Panama, according to the WHO, a total of 3,618 new cases of cancer were reported in 2020, of which 58 cases were esophageal cancer (0.76%), being the 20th most frequent number and 25 people died with this cancer (1.4%) of a total of 3,760 deaths [2]. In North American and European countries, esophageal adenocarcinoma is more

common, where obesity and gastroesophageal reflux are risk factors; however, squamous cell carcinoma of the esophagus is more common in Asia, Africa, and South America. even in countries like India, it is the second most common cause of cancer in men and the 4th leading cause of cancer death and its main risk factor is the use of alcohol and tobacco [3] Esophageal cancer is associated with a poor prognosis and has a fatality rate of 90%, this despite positive advances in treatment, and is due, in many cases, to the fact that it is diagnosed when it is already in an advanced stage, but when they are diagnosed in early stages they can be cured and have a survival rate of 90% at 5 years [4-6].

For patients who have locally advanced squamous cell cancer of the esophagus that cannot be removed or is metastatic, the combination of ciplastin and 5-fluorouracil is most often used, but taxanes such as docetaxel and paclitaxel combined with radiation therapy can also be given. In addition, it has recently been reported that the 3-drug regimen (docetaxel, ciplastine, and 5-fluorouracil) has a treatment response of 62% [7]. Combination therapy produced a 5-year overall survival of 14% [8]. The highest radiation dose did not increase survival or local or regional control in treated patients, but an increase in high-dose treatment-related mortality was observed [9].

In Panama there is no information on patients with locally advanced esophageal cancer who are treated with chemotherapy (CT) and radiotherapy (RT) concomitantly and for this reason it is necessary to share our experience. With this information we seek to evaluate the results of patients with locally advanced esophageal cancer, in this sense, survival, prognostic factors and adverse events of patients in our center who undergo concomitant CT/RT therapy are sought. All of the above with the aim of establishing the efficacy of said protocol in these patients.

2. Material and Methods

Retrospective, cross-sectional observational study whose data were obtained from the electronic records of patients with Locally Advanced Esophageal Cancer who received concomitant CT/RT treatment and were treated at the National Oncology Institute of Panama (ION) between January 2012 and March 2022. The data Electronic records, the ION database and the Mosaiq database were extracted from Oncofarmis, with the prior consent of the institutional authorities. The primary objective of our study was to evaluate the survival results, both in terms of time to progression (TTP) and overall survival (OS), of patients with locally advanced esophageal cancer treated at our institution.

2.1. Patient Selection

The following inclusion criteria were used in this study:

1) Patients older than 18 years.
2) Diagnosis of locally advanced esophageal cancer with histopathological confirmation reviewed at the ION.

The following exclusion criteria were used in this study:

1) Patients who did not receive definitive QT/RT treatment.
2) Patient with demonstrated metastatic disease during the course of definitive treatment.
3) Histologies not squamous cell or adenocarcinoma.

Progression-free survival was defined as the time in months between the start of treatment and disease progression, and overall survival as the time in months between the start of treatment and death or end of study.

2.2. Patient Follow-up

The patients were followed up every week with appointments with their oncologist and every 3 weeks with the treating radiation oncologist, who evaluated the possible adverse effects of the treatment. Tomographic studies and upper gastrointestinal endoscopy were performed 3 months after completing the scheduled treatment.

2.3. Statistical Analysis

Data were collected and analyzed using IBM SPSS Statistics version 23 and Stata 17. Patient characteristics were reported using frequency and descriptive statistics. The Kaplan-Meier method was used to analyze progression-free and overall survival.

3. Results

The study sample consisted of 94 patients diagnosed with locally advanced esophageal cancer treated with CT and RT from January 2012 to March 2022 at the ION, with an average age of 66 years (range 36 to 90). Of these patients, the affected region of the esophagus was 56% lower third, 30% middle third and 14% upper third.

It should be taken into account that 89% of the patients had squamous histology and 11% had adenocarcinoma histology. In total, 35.1% received induction CT, after the start of RT treatment the concomitance was received with a scheme based on carboplatin plus weekly paclitaxel in 41.5% and with a scheme of Cisplatin + 5 Fluorouracil in 34%, the rest were other treatment schemes. It must be taken into account that 66% of the patients received a dose ≥ 45 Gy, with a protraction time of 5 weeks. (See Table 1)

Table 1. *Patient Characteristics.*

Line of treatment	No: 94	%
Carboplatin + Weekly Paclitaxel	38	41.50%
Cisplatin + 5 Fluorouracil	32	34%
Other schemes	24	24.50%
Eastern Cooperative Oncology Group (ECOG)		
0	18	19.10%
1	65	69.10%
2	11	11.80%
Radiotherapy Dose ≥ 45 Gy:	62	66%
Radiotherapy Boost:	39	41.4%
Gastrostomy:	38	40%
Stent placement:	27	28.70%
Histological Differentiation Grade		
Well differentiated	16	17%
Moderately differentiated	52	55.30%
Poorly differentiated	26	27.30%

3.1. Survival and Response Rate

The objective response rate (Partial Response (PR) + Complete Response (CR)) was 26.6%, with a clinical benefit (PR + CR + Stable Disease (SD)) of 36.2%. Disease progression was confirmed in 37.2% of patients. (Table 2). Median Time to Progression of our patients was 6 months and the median overall survival was 9 months (Figures 1 and 2).

Table 2. *Post Treatment Radiographic Response.*

	No: 94	%
Complete Response (CR):	20	21.30%
Partial Response (PR):	6	6.40%
Stable Disease (SD):	8	8.50%
Progression Disease (PD):	35	37.20%
Not Consigned:	25	26.60%
Objective response rate (ORR):	26	27.70%
Clinical Benefit (PR + CR + SD):	34	36.20%

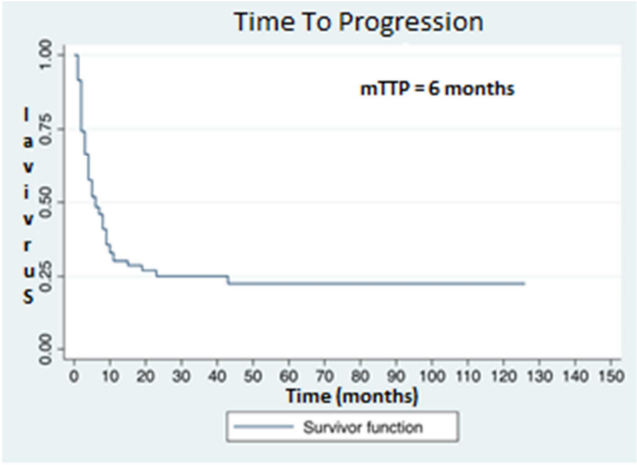

Figure 1. *Time for Progression.*

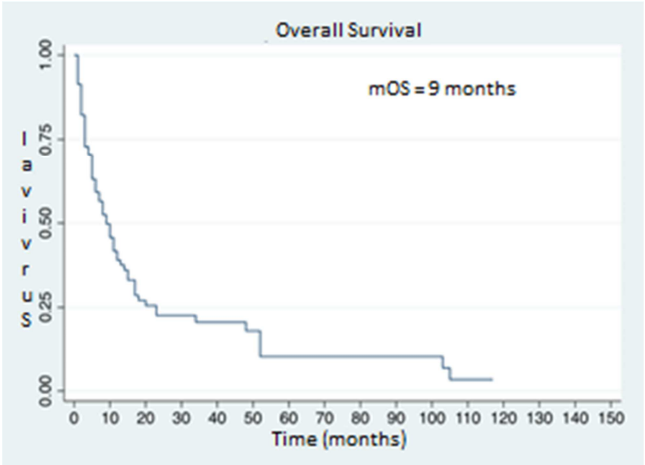

Figure 2. *Overall survival.*

3.2. Adverse Effects

Adverse events were recorded in 39.1% of the patients, and dysphagia was the most common event. 8.3% of patients with adverse events presented neutropenia, followed by nausea, vomiting and weight loss in the same percentage as adverse effects of treatment (Table 3).

Table 3. *Adverse Effects.*

Adverse Event	No: 94	%
dysphagia	15	16%
Neutropenia	8	8.30%
nausea and vomiting	7	7.40%
weightloss	7	7.40%

4. Discussion

This study reports the experience of the ION in the treatment of CT and RT for patients with madly advanced esophageal cancer from January 2012 to March 2022.

The median Time to Progression (TTP) was 6 months and the median overall survival (OS) was 9 months. When compared with other studies such as the Li LQ study [10] our results are more similar to the control arm than just received RT, as in the Herskovic study [11]. Unlike the aforementioned studies, ours is retrospective, treatment was administered even to T4 patients and with high nodal load, which is a type of patient not included in previous studies. In addition, we more frequently used the concomitant CT scheme of carboplatin with paclitaxel, instead of cisplatin with 5FU. In a study that compared the combination of chemoradiotherapy with docetaxel, cisplatin and 5-fluorouracil versus cisplatin and 5-fluorouracil as a combination as chemoradiotherapy found better overall survival (32.8% vs 8.5%) and complete response (36.7% vs 3.7%) in the first group [12]. When evaluating prognostic factors related to survival, we found that the ECOG and the histological grade are related to the OS results, with around 12% of patients presenting an ECOG 2, without being the best candidates for multimodal therapies.

Our follow-up period of the patients was about 10 years. The response rate was 27.7%, being below the results in other retrospective study, in which response rates ranged from 49% [13]. In another study that compared chemoradiotherapy with chemotherapy, it was found that those in the first group had a better complete histological response (40% vs 17%), as well as fewer adverse effects [14]. 39% of our patients presented adverse events, mainly dysphagia followed by neutropenia and in the same proportion gastrointestinal symptoms, such as nausea and vomiting and weight loss, coinciding with results such as the Herskovic study [11] where up to 44% of cases presented adverse events of which the most frequent were haematological and gastrointestinal, which implies that tolerance to treatment is not different from that observed in other studies. Regarding the characteristics of the patients, squamous cell carcinoma, male sex and ECOG 1 were the most frequent among the patients. About 70% of the patients received standard doses of RT, the minority required placement of an esophageal stent to ensure a feeding pathway, and the minority received a boost to the tumor bed beyond standard RT. It is striking that the most widely used QT

scheme was carboplatin plus paclitaxel instead of cisplatin with 5FU, however, during the pandemic we dedicated ourselves to using schemes that required less hospitalization and greater outpatient management, something that the scheme of carboplatin plus weekly paclitaxel provided us with.

Also, in a study comparing definitive chemoradiotherapy with or without esophagectomy found that patients with the surgical procedure had better survival compared to those who did not, the authors concluded that surgery remains an important component in these patients [15]; this aspect was not evaluated in this study, but it is important for future research.

Our study has the following limitations: First, this is a retrospective study from a single center in Panama. Esophageal cancer has a high lethality since most patients debut in advanced stages with bulky disease, which could explain the difference in the results found in our study compared to the literature consulted. However, this study is important for our institution, since it puts the reality of managing locally advanced esophageal cancer in context, generates hypotheses for future research, and suggests a better choice of patients who are going to receive multimodal therapies such as concomitant CT.

5. Conclusions

In this retrospective analysis, we found a median TTP of 6 months and a median OS of 9 months, which are below the survival values evaluated in the international literature, which makes us rethink that we must be more selective with the patients. when offering treatment. The ECOG and the degree of differentiation were the factors associated with a better OS. Hematological and gastrointestinal adverse events were the most reported and these are similar in the review carried out. As previously mentioned, it is important to choose patients in the best clinical conditions for concomitant treatment with CT/RT in order to obtain a better clinical result from the oncological point of view.

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