research article

Definitive radiochemotherapy in esophageal cancer - a single institution experience

Franc Anderluh, Miha Toplak, Vaneja Velenik, Irena Oblak, Ajra Secerov Ermenc, Ana Jeromen Peressutti, Jasna But-Hadzic, Marija Skoblar Vidmar

Department of Radiotherapy, Institute of Oncology Ljubljana; Ljubljana, Slovenia

Radiol Oncol 2019; 53(4): 480-487.

Received 22 March 2019
Accepted 20 September 2019

Correspondence to: Anderluh Franc, M.D., M.Sc., Institute of Oncology Ljubljana, Zaloška 2, SI-1000 Ljubljana, Slovenia.
E-mail: fanderluh@onko-i.si

Disclosure: No potential conflicts of ineterst were disclosed.

Background. Definitive radiochemotherapy is the preferred treatment option in patients with the cancer of the cervical esophagus and a viable treatment option in patients with the cancer of lower two thirds of the esophagus, who decline proposed surgical treatment. The purpose of the study was to evaluate the treatment results with definitive radiochemotherapy of patients with esophageal cancer, treated in a single institution in the period from 2010 to 2017.

Patients and methods. All available medical data for 55 patients with esophageal cancer, who were treated with definitive radiochemotherapy with curative intent, were analyzed retrospectively. Patients were irradiated to a total dose to the tumor of 70 Gy (2 Gy per fraction) in upper third (cervical) tumors or to the mean total dose of 57.6 Gy (1.8 Gy per fraction) in middle third (intrathoracic) tumors. All but one patient received concomitant chemotherapy, with the majority of them (41 patients; 74.5%) receiving concomitant chemotherapy with 5-fluorouracil in continuous 96 hours infusion and cisplatin. The main endpoints of the study were overall survival (OS; death of any cause), loco-regional control (LRC; local and/or regional disease recurrence) and disease-free survival (DFS; recurrence of any kind and/or new primary malignoma). Univariate analysis testing the impact of different parameters on survivals and analysis of treatment related side effects were performed as well.

Results. The mean age of patients was 62 years (SD 9 years; range: 29–80 years). Majority of them had squamous cell cancer (53 patients; 96.4%) in the stage T3 or T4 (47 patients; 85.5%) and/or N+ disease (35 patients; 63.6%). Median follow-up time for the whole group of patients was 16.8 months (range: 0.3–81.8 months). At the time of analysis 14 (25.5%) patients were still alive. Rates for OS, LRC and DFS at two and five years were as follows: 47% and 19.4%; 43.7% and 41%; 32.1% and 11.5%, respectively.

Conclusions. The study results of treatment with definitive radiochemotherapy in patients with esophageal cancer are similar to the results of other studies. Majority of patients ended the treatment according to the protocol, which at least in part can be attributed to the adequate and well organized supportive treatment in our institution.

Key words: esophageal cancer; definitive radiochemotherapy; survival; loco-regional control

Introduction

Nowadays, the preoperative radiochemotherapy (pRCT) followed by surgery is the standard treatment for squamous cell cancer and adenocarcinoma of the esophagus in the stage ≥ T1b–2N0M0, with perioperative chemotherapy being one of the treatment options for adenocarcinoma, as well.[1,2] Based on the results of the RTOG 85-01 study, since the late nineties of the last century, definitive radiochemotherapy (dRCT) became another viable treatment option for patients with locoregionally advanced esophageal cancer.[3] It is reserved for the patients who are not fit for surgery or decline it and is a preferable treatment option for patients with tumors located in the upper third of the esophagus (cervical tumors), since surgery procedures in these patients can be associated with significant postoperative morbidity and mortality.[1,2] Before that, patients with inoperable esophageal cancer

were usually treated with paliative intent or best supportive care only. Survival results for pRCT followed by surgery can reach up to 50% at five years with a locoregional control rate of up to 85%.[4] For dRCT five year survival is around 25% and locoregional control is about 40–60%.[5] In recent years, in patients treated with dCRT, there was not much improvement in survivals, but with multidisciplinary approach, use of modern radiotherapy techniques (such as intensity modulated radiotherapy [IMRT] or volumetric arc therapy [VMAT]) and different chemotherapy regimens given (paclitaxel/carboplatin), there was improvement in reducing treatment related toxicity with consequent better quality of life during and after the treatment.[1,2,6-8]

In Slovenia, in all newly diagnosed esophageal cancer patients, the treatment decisions are provided by multidisciplinary board committees. If the treatment with radical intent is proposed, all the patients are treated in the Institute of Oncology Ljubljana (IOL) which provides the chemo- and radiotherapy part of the treatment protocols and/or in the University Clinical Centers in Ljubljana and Maribor, where surgical procedures are performed. The selection of patients suitable for dCRT is based on the results of pretreatment diagnostic procedures (tumor location, histology, TNM stage), performance stage (WHO stage ≤ 2) and eventual comorbidities (*e.g.* significant renal, hepatic or bone marrow impairment), which could have an impact on the chemotherapy given.

The aim of this retrospective study was to evaluate the treatment results of dRCT for patients treated in the IOL in the period from the beginning of 2010 to the end of 2017.

Patients and methods

Patients and tumors

According to the data of Cancer Registry of Republic of Slovenia and hospital based Cancer Registry of the IOL, in the period from 2010 to 2017, 412 new patients with esophageal cancer were referred for the treatment to the IOL. Of these, based on the multidisciplinary board committee's decision, 55 (13.3%) patients were treated with dRCT with curative intent. Others were treated with pRCT, systemic treatment only or with palliative intent. All available medical data (including demographical data, pretreatment characteristics, treatment specifics and treatment related side effects) of patients treated with dCRT were collected retrospectively. The TNM stage was based on NCCN 7th tumor staging edition. In 1 (1.8%) patient the disease was staged as M1 with neck lymph nodes considered as metastatic, all other patients had a non-metastatic disease. At the start of the treatment 8 (14.5%) patients had synchronous esophageal and different head and neck cancers and 1 (1.8%) patient had synchronous esophageal and operable colon cancers.

Radiotherapy and chemotherapy

All patients were treated on one of IOL's linear accelerators with high energy photons. The total dose to the tumor was defined according to the position of the primary tumor. Patients with tumors located exclusively in the upper third of the esophagus (cervical tumors) were irradiated to the total dose of 70 Gy (2 Gy per fraction), whereas in patients with the intrathoracic tumors (middle third), the prescribed median total dose to the primary tumor was 57.6 Gy in 1.8 Gy per fraction. The radiation techniques varied according to the time period: 3-D treatment planning was used for patients treated in 2010 and the first half of 2011, IMRT technique with single dose level to the planning target volume from the second half of 2011 onward and VMAT or IMRT with synchronous integrated boost (IMRT-SIB) techniques with two or three dose levels for patients treated from 2015 onward. All but one patient received some sort of concomitant chemotherapy, as well. The sort and intensity of the applied chemotherapy varied according to patients' general condition and comorbidities or eventual synchronous cancer.

Endpoints

The main endpoints of the study were overall survival (OS; death of any cause), locoregional control (LRC; local and/or regional disease recurrence) and disease-free survival (DFS; recurrence of any kind and/or new primary malignoma). Data on treatment related side effects were analyzed as well.

Statistics

Statistical analysis was performed using software statistical package SPSS (SPSS Inc., USA). The survival of patients was computed from the date of diagnosis to the close-out date (February 8th, 2019). Survival probability was calculated using Kaplan-Meyer estimate. Univariate analysis was performed as well, with log-rank test used to evaluate the differences between individual groups of

patients and p-value of ≤ 0.05 considered as statistically significant. If any of tested parameters would prove as statistically significant, multivariate analysis (with 95% confidence intervals specified and risk ratios calculated) was planned as well.

The study was approved by the Institutional Review Board Committee and has been conducted in accordance with the declaration of Helsinki.

Results

Patients and tumors

The mean age of 55 patients included in the study was 62 years (SD 9 years, range: 29-80 years). Majority of patients were male (45 patients – 81.8%) in a good performance status (WHO performance stage 0-1 in 50 patients – 90.9%) and had squamous cell cancer (53 patients - 96.4%) in the stage T3 or T4 (47 patients - 85.5%) and/or N+ disease (35 patients - 63.6%). Patients' and tumors' characteristics are presented in Table 1.

The mean time from the onset of symptoms to diagnosis was 17.2 weeks (range 4–56 weeks). At diagnosis 4 (7.3%) patients had no problems swallowing, 11 (20%) had problems with swallowing solid food, 32 (58.1%) could only swallow soft food or liquids, 6 (10.9%) were aphagic and for 2 (3.6%) patients no data on swallowing status was available. Before the start of dRCT 33 (60%) patients needed surgical intervention for establishing the adequate nutritional pathway; in 1 dilation of primary tumor's stenosis was performed, in 6 patients an esophageal stent was placed on the site of the primary tumor and in 26 patients gastric or jejunal feeding tube was inserted. In 6 (10.9%) patients no weight loss was detected before the start of the specific treatment, 11 (20%) patients lost ≤ 5% of the baseline weight, 8 (14.5%) patients lost 5–10% of the baseline weight and 24 (34.6%) patients lost > 10% of the baseline weight. All patients were presented at the multidisciplinary board committee for the decision on the sort of specific treatment. The median time from diagnosis to the start of any kind of specific treatment was 5.7 weeks (range: 2–18.6 weeks).

TABLE 1. Patients' and tumors' characteristics

	N (%)
Gender	
male	45 (81.8)
female	10 (18.2)
Age at diagnosis (years)	mean: 62 (SD 9 years, range: 29–80 years)
WHO performance stage	
0	24 (43.6)
1	26 (47.3)
2	5 (9.1)
Risk factors	
none	13 (23.6)
active or ex-smokers	31 (56.4)
gastroesophageal reflux	2 (3.6)
gastroesophageal reflux and smoking	3 (5.5)
unknown	6 (10.9)
T stage	
T X	1 (1.8)
T 1	1 (1.8)
T 2	6 (10.9)
T 3	36 (65.5)
T 4	11 (20)
N stage	
N 0	20 (36.4)
N 1	20 (36.4)
N 2	12 (21.8)
N 3	3 (5.5)
Histology	
squamous cell cancer	53 (96.4)
adenocarcinoma	1 (1.8)
verified carcinoma, unspecified	1 (1.8)
Grade	
G 1	3 (5.5)
G 2	28 (50.9)
G 3	12 (21.8)
unknown or not specified	12 (21.8)
Upper border of the tumor	
≤ 18 cm from the incisors	32 (58.2)
18–32 cm from the incisors	23 (41.8)

SD = standard deviation

Radiochemotherapy

Definitive radiochemotherapy was advised by multidisciplinary board committee in 49 (89.1%) patients and in 6 (10.9%) patients pRCT was proposed. In these 6 patients, after completion of the preoperative treatment with radiochemotherapy with the total dose of 45 Gy (1.8 Gy per fraction) to the tumor bed, 1 patient refused the proposed surgical procedure and in the remaining 5 patients, the surgery was declined according to thoracic surgeons' decisions based on evaluation diagnostic procedures. Four patients were treated with additional radiochemotherapy and in 2 patients only careful follow up was advised. The radiation techniques used were as follows: in 6 (12.2%) patients 3-D treatment planning was used, in 11 (22.4) patients IMRT and in 32 (58.1%) patients VMAT or IMRT-SIB, respectively. PET-CT for treatment planning was used in 25 (45.5%) patients. Median total radiation dose applied to the tumor bed was 57.6 Gy (range: 23.4–70 Gy), the median number of fractions was 32 (range: 13–36 fractions) and the median duration of the radiotherapy treatment was 45 days (range: 17–57 days). In none of the patients, the correction of total dose to the tumor bed due to

TABLE 2. Different chemotherapy regimens used

Chemotherapy regimen used	N (%)
5-FU in continuous 96 hours infusion + cisplatin	41 (74.5)
Weekly cisplatin only during RT	3 (5.5)
Paclitaxel + carboplatin	2 (3.6)
5-FU + carboplatin	2 (3.6)
Induction TCF followed by weekly cisplatin during RT	1 (1.8)
Induction 5-FU + cisplatin followed by weekly carboplatin during RT	1 (1.8)
Induction paclitaxel + carboplatin followed by weekly carboplatin during RT	1 (1.8)
Induction weekly cisplatin followed by weekly carboplatin during RT	1 (1.8)
Induction paclitaxel + carboplatin followed by 5-FU + cisplatin during RT	1 (1.8)
Induction capecitabine + cisplatin followed by weekly cisplatin during RT	1 (1.8)
No chemotherapy given	1 (1.8)

FU = fluorouracil; RT = radiotherapy; TCF = docetaxel, cisplatin and 5-FU

TABLE 3. Side effects of concomitant radiochemotherapy (according to EORTC Common Toxicity Criteria version 4)

Side effect	Grade			
	0	1	2	3
Esophagitis	6 (10.9)	21 (38.2)	17 (30.9)	10 (18.2)
Radiodermatitis	35 (63.3)	8 (14.5)	7 (12.7)	4 (7.3)
Nausea	40 (72.7)	9 (16.4)	4 (7.3)	1 (1.8)
Vomiting	50 (90.9)	1 (1.8)	3 (5.5)	0
Neutropenia	25 (45.5)	8 (14.5)	10 (18.2)	12 (21.8)
Thrombocytopenia	20 (36.4)	21 (38.2)	8 (14.5)	6 (10.9)
Anemia	6 (10.9)	27 (49.1)	21 (38.2)	1 (1.8)

TABLE 4. Median, two- and five years survivals

	OS	LRC	DFS
Median	20.5 months (95% CI 8.2–32.8)	16.6 months (95% CI 7.3–26)	12.9 months (95% CI 9.8-16.1)
2-year	47%	43.7%	32.1%
5-year	19.4%	41%	11.5%

CI = confidence interval; DFS = disease-free survival; LRC = locoregional control; OS = overall survival

toxic side effects of the treatment was needed. One patient finished the intended treatment prematurely after receiving 23.4 Gy because of severe deterioration of general performance status due to comorbidities and continued with palliative treatment in a regional general hospital. Another patient finished with radiochemotherapy prematurely after receiving the dose of 48 Gy due to esophagus perforation, which in our opinion was not attributed to the treatment received but was one of the possible rare complications in the natural course of the disease. All, but 1 patient also received some sort of concomitant chemotherapy, with the majority of them (41 patients; 74.5%) receiving concomitant chemotherapy with 5-fluorouracil (5-FU) in continuous 96 hours infusion and cisplatin. Ten different chemotherapy regimens used are presented in Table 2. The median number of chemotherapy applications received was 3 (range: 0–8 applications). In 45 (81.8%) patients no adjustment of the dose or number of chemotherapy applications was needed, whereas in the remaining 9 (16.4%) patients chemotherapy regimen was adjusted due to treatment toxic side effects (renal impairment and/or neutropenia and/or thrombocytopenia).

Treatment side effects, which were graded according to EORTC Common Terminology Criteria for Adverse Events (CTCAE) version 4, are presented in Table 3.[9] At least one side effect of concomitant radiochemotherapy of any grade was recorded in all patients. Twenty-two (40%) patients had at least one side effect of grade III, with most common side effects of grade III being neutropenia in 12 (21.8%) and esophagitis in 10 (18.2%) patients. One treatment related death was recorded immediately after the completion of radiotherapy treatment due to fistula formation on the place of esophageal stent inserted before the start of radiochemotherapy, with consequent massive bilateral bronchopneumonia and cardiorespiratory failure.

Because of the treatment related side effects and/or severe deterioration of alimentary status 33 (60%) patients were hospitalized during radiotherapy for supportive treatment. During the treatment 25 (45.5%) patients received peroral nutritional supplements, 29 (52.7%) parenteral supplements and 1 (1.8%) patient didn't need any kind of nutritional support. Based on the weight at the start of the treatment, at the end of the specific treatment, no weight loss was recorded in 18 (32.7%) patients, 17 (30.9%) patients lost ≤ 5% of the weight, 7 (12.7%) patients 5–10% of the weight and in 9 (16.4%) patients the weight loss of > 10% was recorded. No data on the weight loss during the treatment was available in 4 (7.3%) patients. During or after the completion of dRCT 16 (29.2%) patients needed surgical intervention; in 4 dilation on the place of primary tumor was performed, in 3 esophageal stent was placed on the site of the pri-

TABLE 5. Results of univariate analysis testing the impact of different parameters on survivals

	OS (p)	LRC (p)	DFS (p)
Gender: male (N = 45) female (N = 10)	0.16	0.46	0.63
Age: ≤ 62 years (N = 29) > 62 years (N = 26)	0.16	0.6	0.85
WHO performance stage: 0–1 (N = 50) 2 (N = 5)	0.99	0.78	0.95
Risk factors: none present (N = 19) at least one present (N = 36)	0.67	0.24	0.23
Tumor localization: upper third - cervical (N = 32) middle third - intrathoracic (N = 23)	0.18	0.56	0.57
T stage: T 1+2 (N = 8) T 3+4 (N = 47)	0.38	0.76	0.37
N stage: N0 (N = 20) N+ (N = 35)	0.79	0.22	0.42
Treatment schedule: definitive radiochemotherapy (N = 49) preoperative radiochemotherapy without surgery and completion of the treatment with additional radio(chemo) therapy (N = 6)	0.66	0.55	0.46
TD on tumor: ≤ 57.6 Gy (N = 35) > 57.6 Gy (N = 20)	0.61	0.52	0.79

DFS = disease-free survival; LRC = locoregional control; OS = overall survival; p = p value; TD = total dose

mary tumor, in 1 patient a stent was placed in the trachea due to the formation of tracheoesophageal fistula and in 8 patients gastric or jejunal feeding tube was inserted.

Survival

Median follow-up time for the whole group of patients was 16.8 months (range: 0.3–81.8 months). At the time of analysis 14 (25.5%) patients were still alive. Of 41 (74.5%) patients who died, 31 died due to the esophageal cancer, 6 of other causes and for 4 patients no data on the cause of death was available. Median survivals and survivals at two and five years are presented in Table 4 and survival curves in Figures 1–3.

In univariate analysis none of the tested parameters reached statistical significance for their impact on survivals (Table 5). Therefore, multivariate analysis was not performed.

After the end of the treatment, the recurrence of the disease was recorded in 35 (63.6%) patients in the median time of 6.2 months (range: 0–57.8 months). The disease recurred locally in 26 (72.2%) patients, regionally in 15 (42.8%) patients and in 14 (40%) patients systemic spread was detected. Ten (28.6%) patients received some sort of additional specific treatment and in others best supportive care was advised by the multidisciplinary board committee.

Discussion

Esophageal cancer is a disease which predominantly affects older men with a history of smoking and alcohol abuse (squamous cell cancer) or patients with obesity and history of gastroesophageal reflux and/or Barret's esophageal metaplasia (adenocarcinoma).[7] Nowadays, dRCT is one of the possible treatment strategies used in esophageal cancer of both histologies. The indications for its use are well defined in national and international guidelines for the treatment of patients with esophageal cancer.[1,2,10] It is reserved for patients with inoperable tumors of the lower two thirds of the esophagus, patients who decline surgery and is a preferable treatment option in patients with tumors located in the cervical esophagus. Since dRCT can be accompanied by serious treatment side-effects, the careful selection of patients is necessary. In our group of patients, 58.2% of them had tumors in the cervical esophagus and/or synchronous head and neck cancers and in the remaining 23 patients, the tumor was locally advanced (T3 or T4) in 20 (86.9%) patients. 90.9% of all the patients included in our study were in a good general performance (performance stage 0-1 according to WHO scale). In the retrospective study of Haefner *et al*. in the group of 93 patients treated with dCRT the tumor was located in cervical, upper or mid esophagus in 66.7% of patients.[11] Seventy-two (77.2%) patients had T3-4 tumors and most of them were in a relatively good general condition with the mean Karnofsky performance status of 86 (range: 70–100).

Because of the natural course of the disease which primarily affects the swallowing, special attention needs to be addressed to patients' pretreatment evaluation of alimentary status and adequate nutritional support during the treatment.[12] In our group of patients, 49 (89.1%) patients had problems with swallowing and/or were aphagic at diagnosis and consequently in 60% of patients some kind of surgical intervention (dilation or esophageal stent insertion or gastric-/jejunal feeding tube insertion) was needed before the start of dRCT. In the study of Bedenne *et al*., in patients treated with

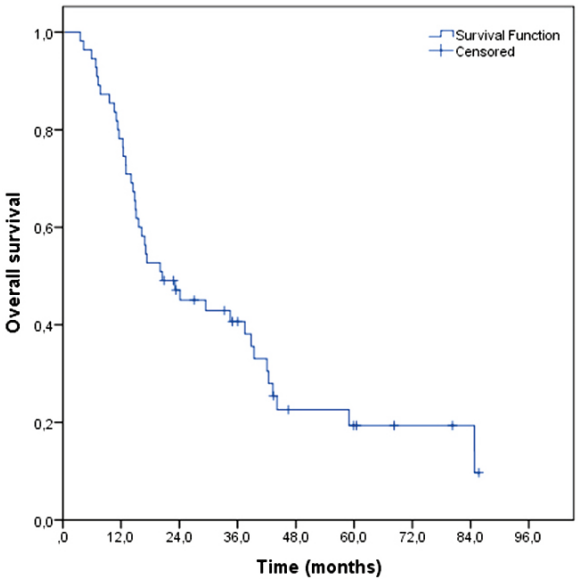

FIGURE 1. Overall survival curve.

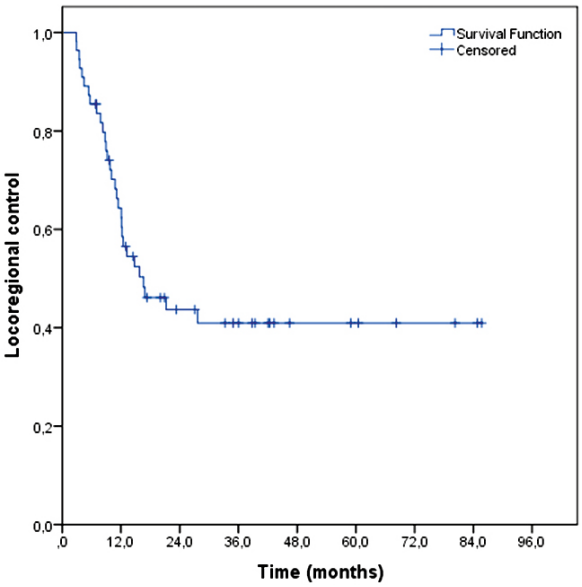

FIGURE 2. Locoregional control curve.

dCRT, 90.8% had problems swallowing before the start of any treatment.[13] However, no data on surgical procedures performed before the start of the treatment to establish adequate nutritional pathway is reported. During dRCT all the patients were carefully monitored by attending physician and the staff of IOL's supportive care Unit for clinical nutrition and diethotherapy, as well. In this way, we were able to select patients who needed special attention. All but one patient received either peroral or parenteral nutritional supplements during treatment and 60% of all the patients were hospitalized during dRCT for appropriate supportive treatment. Good supportive care reflects in the facts that in only 29.1% of all the patients the additional weight loss of >5% was recorded during treatment and that majority of patients could complete their treatment with the intended radiation dose to the primary tumor.

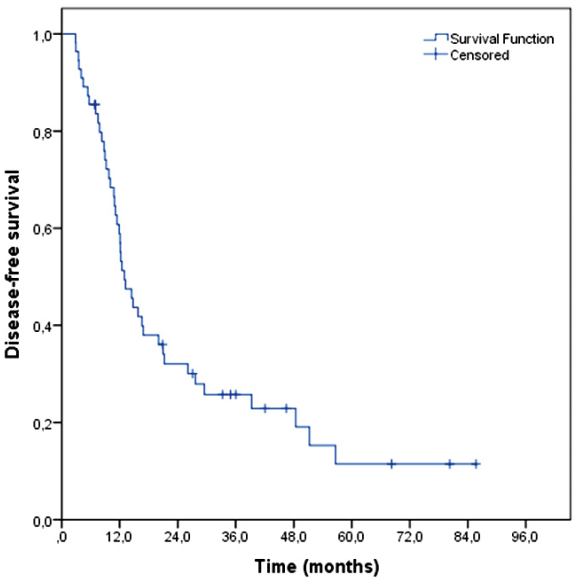

FIGURE 3. Disease-frees survival curve.

All but one patient included in the study received some sort of concomitant chemotherapy during irradiation, with 10 different chemotherapy schedules being used (see Table 2). The sort of chemotherapy used was determined by the multidisciplinary board committee's decision taking into account the extent of the disease, patients' general condition, comorbidities and possible synchronous tumors (8 patients with synchronous esophageal and head and neck cancers and 1 patient with synchronous esophageal and colorectal cancers). The intensity of applied chemotherapy was adjusted because of the comorbidity and/or treatment related side effects (renal impairment and/or changes in blood count) in 16.4% of patients. All others received the dose planned at the start of the treatment, which at least in part can be attributed to the good supportive care during the treatment. Majority of patients (74.5%) in our study received concomitant chemotherapy with 5-FU in continuous 96 hours infusion and cisplatin which in many countries is still the gold standard in dRCT, although according to the results of CROSS trial, nowadays many authors believe that concomitant chemotherapy with paclitaxel and carboplatin should be used in dRCT as well.[6,14]

In our study the total dose of 70 Gy to the primary tumor (in fractions of 2 Gy) was used in patients with tumors located exclusively in the upper third of the esophagus, whereas in patients with cervical tumors which extended in the thorax or with intrathoracic tumors, in order to avoid unacceptable toxicity, different fractionations were used with the median total dose to the primary tumor of 57.6 Gy in 32 fractions. Today, the topic of the radiation dose in dRCT is still controversial and highly debated. In the USA doses of 50-50.4 Gy are advised although many authors believe that, in order to increase the chance of better local control and survival, higher doses to the primary tumor should be used, which indeed is the case in Europe and some other parts of the world. [1,2,5,7,15]

The treatment with dRCT in our group of patients was relatively well tolerated. As expected with such a treatment, in all the patients at least one treatment side effect was recorded (Table 3), with 40% of patients having at least one side effect of grade III. The most common side effects of grade III were neutropenia in 21.8% and esophagitis in 18.2% of patients, which is concordant with the data from the literature.[7,8] However, despite the treatment related side effects and because of good supportive treatment, the tolerability of the treatment in our group of patients was good, since majority of patients received the prescribed radiation dose to the tumor and in only 9 (16.4%) patients any kind of adjustments on the dose and/or number of chemotherapy applications were needed. One treatment related death was recorded at the end of dRCT in the patient in whom tracheoesophageal fistula formed on the place of esophageal stent inserted before the start of the dRCT. The problem of dose perturbations in the area of inserted metallic stents is well known.[16] In our opinion, due to the relatively high radiation dose applied to the primary tumor, insertion of metallic stents before the start of the dRCT should be avoided. However, since no clinical reports on effects of stents on radiotherapy dose distribution in esophageal cancer exist, any clinical recommendations should be made with caution.

The OS in our group of patients (19.4% - see Table 4) was a bit lower if compared with the results from the literature, according to which the 5-years OS after dRCT is around 25%. On the other hand, 5-year LRC of 41% in our study, is concordant with the data from the literature with 5-year LRC after dRCT of 40-60%.[3,17-20] The slightly lower OS in our study can be attributed to unfavourable stage distribution since 85.5% of our patients had T3 or T4 disease and 63.6% N+ disease and the fact that of 35 patients in whom the recurrence of the disease was recorded, only 10 patients received some sort of additional specific treatment. In esophageal cancer some of the factors (such us gender, age at diagnosis, T and N stage, WHO performance stage, radiation dose received, etc.) are well recognized as the risk factors for worse treatment outcome.[7,21,22] However, in our study in univariate analysis none of the analyzed factors reached statistical significance for their impact on survivals, which in our opinion can be attributed to relatively small overall number of patients and uneven distribution of patients in different subgroups tested.

Conclusions

Our results of treatment with definitive radiochemotherapy in patients with esophageal cancer are concordant with the results of other studies. Due to the high intensity of existing treatment protocols, multidisciplinary approach with adequate supportive treatment is needed, and in our opinion treatment of patients with dCRT should be centralized and performed in institutions with sufficient experience and workload. Majority of our patients ended the treatment according to the protocol, which at least in part can be attributed to the adequate and well organized supportive treatment in our institution. However, the results of dRCT in general are still not satisfactory. With the increasingly widespread use of modern radiotherapy treatment techniques, such as IMRT or VMAT, there is not much room for improvement in radiotherapy part of the treatment protocols. Most probably there is still room for improvement in systemic treatment in means of intensifying chemotherapeutics given and/or with the addition of target drugs and immunotherapy, but further prospective studies addresing this subject are needed.

References

1. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Esophageal and esophagogastric junction cancers, version 1. 2019. [cited 2019 Jan 15]. Available at: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
2. Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; **27(Suppl 5):** v50-7. doi: 10.1093/annonc/mdw329
3. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA, Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999; **281:** 1623-7. doi: 10.1001/jama.281.17.1623

4. van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BPL, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366:** 2074-84. doi: 10.1056/NEJMoa1112088

5. Jeene PM, van Laarhoven HWM, Hulshof MCCM. The role of definitive chemoradiation in patients with non-metastatic oesophageal cancer. *Best Pract Res Clin Gastroenterol* 2018; **36-37:** 53-9. doi: 10.1016/j.bpg.2018.11.011

6. Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015; **16:** 1090-8. doi: 10.1016/S1470-2045(15)00040-6

7. Czito BG, DeNittis AS, Palta M. Esophageal Cancer. In: Halperin EC, Wazer DE, Perez CA, Brady LW, editors. *Principles and practice of radiation oncology*. 6th edition. Philadelphia: Lippincott Williams&Wilkins; 2013. p. 995-1023.

8. Adebahr S, Schimek-Jasch T, Nestle U, Brunner TB. Oesophagus side effects related to the treatment of oesophageal cancer or radiotherapy of other thoracic malignancies. *Best Pract Res Clin Gastroenterol* 2016; **30:** 565-80. doi: 10.1016/j.bpg.2016.07.003

9. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. [cited 2019 Jan 15]. Available at: https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

10. Guidelines for the treatment of esophageal and esophagogastric junction cancers. [Slovenian]. Anderluh F, But Hadžić J, Crnjac A, Gačevski G, Hlebanja Z, Jeromen A, et al, editors. [cited 2019 Jan 15]. Available at: https://www.onko-i.si/fileadmin/user_upload/Smernice_za_zdravljenje_raka_poziralnika_in_EGS_splet.pdf

11. Haefner MF, Lang K, Verma V, Koerber SA, Uhlmann L, Debus J, et al. Neoadjuvant versus definitive chemoradiotherapy for locally advanced esophageal cancer. Outcomes and patterns of failure. *Strahlentherapie Oncol* 2018; **194:** 116-24. doi: 10.1007/s00066-017-1211-0

12. Jordan T, Mastnak DM, Palamar N, Kozjek NR. Nutritional therapy for patients with esophageal cancer. *Nutr Cancer* 2018; **70:** 23-9. doi: 10.1080/01635581.2017.1374417

13. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9201. *J Clin Oncol* 2007; **25:** 1160-8. doi: 10.1200/JCO.2005.04.7118

14. Tomasello G, Ghidini M, Barni S, Passalacqua R, Petrelli F. Overview of different available chemotherapy regimens combined with radiotherapy for the neoadjuvant and definitive treatment of esophageal cancer. *Expert Rev Clin Pharmacol* 2017; **10:** 649-60. doi: 10.1080/17512433.2017.1313112

15. Luo Y, Mao Q, Wang X, Yu J, Li M. Radiotherapy for esophageal carcinoma: dose, response and survival. *Cancer Manag Res* 2017; **10:** 13-21. doi: 10.2147/CMAR.S144687

16. Li XA, Chibani O, Greenwald B, Suntharalingam M. Radiotherapy dose perturbation of metallic esophageal stents. *Int J Radiat Oncol Biol Phys* 2002; **54:** 1276-85. doi: 10.1016/S0360-3016(02)03803-8

17. Stahl M, Stuschke M, Lehkmann N, Meyer H-J, Walz MK, Seeber S, et.al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005; **23:** 2310-7. doi: 10.1200/JCO.2005.00.034

18. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high dose versus standard-dose radiation therapy. *J Clin Oncol* 2002; **20:** 1167-74. doi: 10.1200/JCO.2002.20.5.1167

19. Versteijne F, van Laarhoven HWM, van Hooft JE, van OS RM, Geijsen ED, van Berge Henegouwen MI, et al. Definitive chemoradiation for patients with inoperable and/or unresectable esophageal cancer: locoregional recurrence pattern. *Dis Esophagus* 2015; **28:** 453-9. doi: 10.1111/dote.12215

20. Teoh AYB, Chiu PWY, Yeung WK, Liu SYW, Wong SKH, Ng EKW. Long-term survival outcomes after definitive chemoradiation versus surgery in patients with resectable squamous carcinoma of the esophagus: results from a randomized controlled trial. *Ann Oncol* 2013; **24:** 165-71. doi: 10.1093/annonc/mds206

21. Huang FL, Yu SJ. Esophageal cancer: Risk factors, genetic association, and treatment. *Asian J Surg* 2018; **41:** 210-5. doi: 10.1016/j.asjsur.2016.10.005

22. Domper Arnal MJ, Ferrandez Arenas A, Lanas Arbeloa A. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. *World J Gastroenterol* 2015; **21:** 7933-43. doi: 10.3748/wjg.v21.i26.7933