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Chemo-radiotherapy in Locally Advanced Squamous Cell Oesophageal Cancer—are Upper Third Tumours more Responsive?

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Abstract Before neoadjuvant therapy was widely applied, the prognosis of oesophageal cancer had been considered dependent on the location of the tumor, i.e. upper third cancers had had the worst prognosis. The aim of this retrolective study was to prove the efficiency of the neoadjuvant treatment, and to compare the response of esophageal cancer in different locations. Between January 1998 and September 2005, 102 patients with locally advanced squamous cell oesophageal cancer received preoperative chemo-radiotherapy. In 40 cases the tumor was located in the upper third and in 62 cases in the middle third of the oesophagus. After a four-week-long treatment free period restaging was carried out and patients considered resectable were submitted to surgery. From 40 patients with upper third oesophageal cancer 28 underwent oesophageal resection or pharyngo-laryngectomy. Thiry-five percent a complete histopathological remission was observed. From 62 patients with middle third oesophageal cancer 43 underwent oesophageal resection. Histological examination of the resected specimens documented complete response only in three patients. The median survival and the R0 resection rate were similar in the two groups. Although the resection rate, perioperative morbidity, mortality and the median survival were similar in the two groups, a significantly higher rate of complete response ($p<0,05$) was observed in patients with upper third oesophageal cancer compared to patients with middle third oesophageal cancer. It seems that upper third oesophageal cancer has superior sensitivity to multimodal treatment therefore our results may support that upper third location is not an unfavorable prognostic factor any more.

Keywords Complete response · Locally advanced tumor · Neoadjuvant therapy · Squamous cell oesophageal cancer

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Introduction

Oesophageal cancer currently ranks ninth among the most frequent cancers in the world [1]. It is well known, that the prognosis of patients with oesophageal cancer is poor, the average 5-year-survival rate after surgical resection is only

3–20% [2], although some highly experienced centers reported much better survival rates [1, 3, 4]. In the treatment of oesophageal cancer the surgical resection is the basis of the curative approach. The most important prognostic factors are the depth of the tumor infiltration (pT), the presence of positive lymph nodes (pN) and the quality of the surgical resection (R0). Patients with locally advanced (T3-T4) cancer have 20–31% 5 years survival rate when the surgical resection was complete (R0), compared to 0% when incomplete resection (R1 or R2) was performed [1]. The major problem is, that most cases are diagnosed at an advanced stage, when the chance of the R0 resection is below 50% and 5 years recurrence rate is high even in case of a curative resection. This poor prognosis is especially true if the tumor is located in the upper third of the oesophagus, because the disease is already irresectable in a less advanced stage, or usually an extended resection is necessary which extremely increases the morbidity and mortality rate. This may explain the common opinion that the higher the position of the tumor the worse the prognosis [5, 6].

But is this statement true in the era of modern neo-adjuvant treatment?

The aim of the current work was to prove the efficiency of the neoadjuvant therapy compared to a historical control group. An other aim was to report our data on the different response of the upper and mid third, locally advanced squamous cell tumors to the neoadjuvant therapy.

Patients and Methods

In the Department of Surgery, Medical Faculty, University of Pécs 382 oesophageal resections were performed due to cancer between Jun. 1992 and Sept. 2005. (cardiac tumors were excluded) However, according to the data that neoadjuvant therapy has favorable effect in the treatment of oesophageal cancer, patients with locally advanced (T3, T4,Nx) squamous cell oesophageal cancer located at or above the tracheal bifurcation were chosen for multimodal therapy from Nov.1997.

In this retrolective (retrospective) study (according to the criteria of Feinstein) [7] any patient who had histologically proven locally advanced oesophageal squamous cell cancer without distant metastases and was considered medically fit for surgery (age<75 years, Karnoffsky score>60%) was eligible, if the tumor was located at or above the tracheal bifurcation. Patients with previous chemo- or radiotherapy in the medical history were excluded. Informed consent was obtained from all patients. In all patients the staging procedures included endoscopy, endoscopic ultrasound, barium swallow, chest X-ray, abdominal and cervical ultrasound, computed tomography (CT) scan and bronchoscopy with brush cytology or biopsy. Between Nov.1997 and Sept. 2005 102 patients were involved. The mean age was 55.5 years, in sex ratio a high male dominance was observed. (90 males:12 females) Following the staging, patients received concomitant chemo-radiotherapy. (Table 1.) After a four-week-long treatment free period restaging was carried out and patients considered resectable were submitted to surgery. Patients were divided into two groups. In Group 1 the tumor was located at the upper third of the oesophagus (above the aortic arch) in Group 2 the carcinoma was located in the mid third of the oesophagus (at or above the tracheal bifurcation) Clinical data are presented in Table 2. To evaluate the response the whole staging procedure detailed above was repeated and then the following classification was used:

Complete remission: significant downsizing of the disease (normal oesophagogram, endoscopy and CT scan) and no viable tumor cell in the histological sample of the resected specimen.
Partial remission: viable tumor cells in the histological evaluation, but the downsizing of the tumor was more then 50%.
Stable disease: tumor regression was less than 50%.
Progression: tumor size increased, fistula formation or distant metastasis appeared.

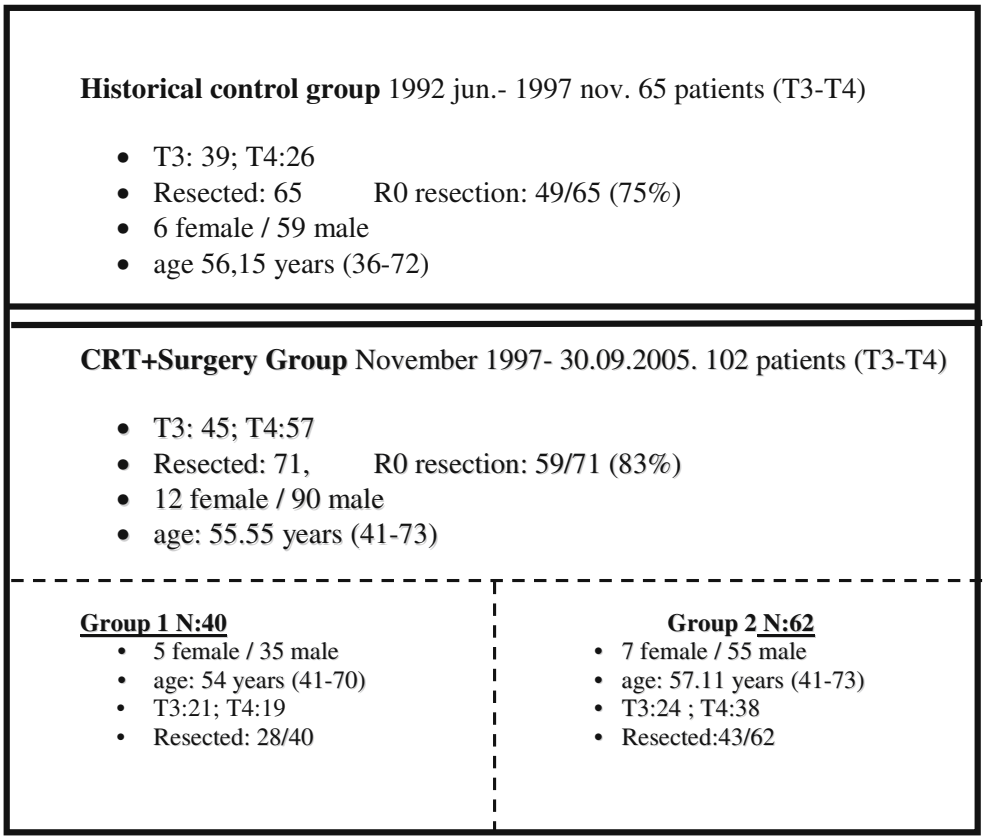
During the surgical procedure patients underwent transthoracic en bloc oesophagectomy with 2-field lymphadenectomy if the tumor was located at the mid third of the oesophagus. Upper third oesophageal cancer was treated with either transhiatal oesophagectomy which was combined with partial pharyngectomy when necessary (larynx preserving pharyngo-oesophagectomy), or pharyngo-laryngectomy with partial oesophageal resection, followed by a free jejunal graft reconstruction, as reported previously [8]. In the other cases the gastrointestinal continuity was restored by gastric pull-up.

As a first step, to prove the efficiency of the preoperative chemo-radiotherapy the neoadjuvant group was compared to a historical control group of 65 patients, who were operated

Table 1 Protocol of the preoperative chemo-radiotherapy

- *1st. day:* radiotherapy + Cisplatin (75mg/m^2) infusion
- *1st-5th day:* radiotherapy +5 FU 1000 mg/m2 with Ca-folinate 20 mg/m2 infusion
- *From 8th day onwards:* radiotherapy alone
- Irradiation with 180 cGy using external beam once daily for 5 days weekly (up to 3,960 cGy)

Table 2 Patients characteristics



on between Jun. 1992 and Nov.1997 with locally advanced squamous cell oesophageal cancer located at or above the tracheal bifurcation. There was no statistically significant difference between the patient groups regarding age, gender, etc. (Table 2) Than in the second step, a survival analysis was performed in the neoadjuvant group, according to the different tumor locations. (upper vs. mid third tumors).

At the statistical analysis quantitative data were expressed as the mean, median and range. Differences between the groups were analyzed by using the chi-square test. Survival rates were calculated according to Kaplan-Meier method and were tested with the log-rank test. Statistical differences were determined by using the log-rank test, all tests were two-sided, and a P value$\leq$0.05 was considered as significant. Analyses were performed using the statistical software SPSS for Windows. (version 11.5; SPSS Inc., Chicago IL)

Results

After the neoadjuvant chemo-radiotherapy (CRT) the response rate was high (70% and 69%) in our both groups. (Figure 1) The histopathological examination of the resected specimens confirmed pathological complete remission (pCR) in 14 patients in Group 1 (50%) and in 3 patients in Group 2 (7%), the difference between the two groups was significant. ($p<0.01$).) The resectability rate was similar in the two groups (70% and 69%). Treatment results are presented in Table 3. In 70% (28/40) of the cases with cervical oesophageal cancer, neoadjuvant chemo-radiotherapy induced partial or complete tumor regression that rendered pharyngo-laryngo-oesophagectomy unnecessary. In 15 cases (37.5%) the tumor disappeared from the pharynx thus larynx preserving oesophagectomy with partial pharyngectomy was performed. In 9 cases when the cancer disappeared only from the cervical oesophagus, a pharyngo-laryngectomy was done. In these cases the pharyngo-laryngectomy was combined with a segmental resection of the cervical oesophagus and for reconstruction a free jejunal transfer was performed. This organ preserving procedure was especially important regarding quality of life aspects [8, 9]. Postoperative mortality was 14% (4/28), and postoperative morbidity was 43% (12/28) in Group 1. In Group 2 postoperative mortality was 18% (8/43) and postoperative morbidity was 62% (27/43). The differences were not significant. During the survival analysis, the multimodal therapy group was compared to a historical control group where surgery was done alone. Mean survival after the neoadjuvant CRT combined with surgery was

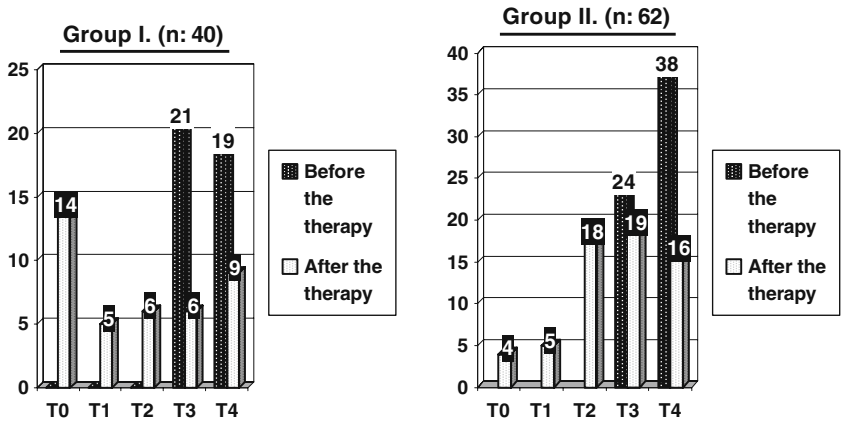


Fig. 1 Response of upper (*Group I*) and middle third (*Group II*) esophageal cancers to CRT

significantly better compared to the surgery alone group. (22.7 months vs 9.3 months p:0.001) (Fig. 2)

The mean survival rate was not influenced by the location of the tumor as it was similar in Group 1 and Group 2. (22.8 months vs 22.1 months, p:0.724) (Fig. 3) However independently from the location, the mean survival of cases with complete remission was significantly longer compared to the other cases. (33 months vs 13.3 months, p:0.024) (Fig. 4)

Discussion

There were 829 new esophageal cancer cases in 2002 in Hungary, and the number of deaths were 709 [2]. In the last decades in western Europe and in the USA a dramatic increase has been observed in the incidence of adenocarcinoma of the oesophagus, while the incidence of squamous cell cancer was stable [1–3]. Although the incidence of oesophageal adenocarcinoma has also increased in Hungary, squamous cell oesophageal cancer remained the dominant type. The importance of this lies in the fact that the prognosis of squamous cell cancer is well known worse than that of adenocarcinoma [3].

Despite the substantial progress in oesophageal cancer therapy, the overall prognosis of these patients has not improved significantly in the past two decades. At the time of the diagnosis nearly one third of the patients are not feasible for any curative treatment, and most of the remainder have locally advanced disease. An anatomical factor, which is supposed to be responsible for this poor prognosis, is the lack of serosa layer. Therefore the tumor

Table 3 Treatment results and complications

GROUP I. (N:40)		GROUP II. (N:62)	
RESPONSE			
Complete remission:	14	Complete remission:	3
Partial remission:	14	Partial remission:	40
Stable disease:	8	Stable disease:	8
Progression:	4	Progression:	11
TREATMENT RESULTS			
Surgery:	33/40	Surgery:	49/62
Exploration:	5	Exploration:	6
Resection:	28/40	Resection:	43/62
R0 resection:	23/28	R0 resection:	36/43
COMPLICATIONS			
Perioperative mortality	4/28 (14%)	**Perioperative mortality**	8/43 (18%)
Perioperative morbidity	12/28 (43%)	**Perioperative morbidity**	27/43 (62%)
Anastomosis leakage	4/28 (14.3%)	Anastomosis leakage	7/43 (16.3%)
Pulmonary complications	5/28 (17.8%)	Pulmonary complications	15/43 (34.9%)
Other	3/28 (10,7%)	Other	5/43 (11.6%)
In Hospital stay (days))	17.75 (10–54	**In Hospital stay (days)**	17.33 (9–47)

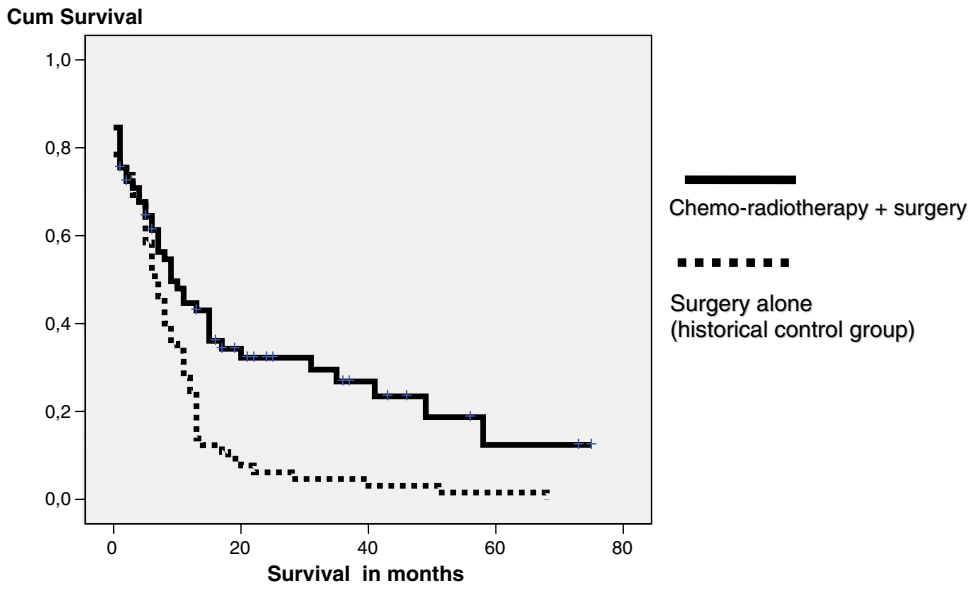


Fig. 2 Survival after neoadjuvant CRT combined with surgery was significantly better compared to surgery alone

	Mean(a)				Median			
	Estimate	Std. Error	95% C I		Estimate	Std. Error	95% C Interval	
			Lower	Upper			Lower	Upper
Surg	9,292	1,452	6,447	12,138	7,000	1,005	5,031	8,969
Surg+CRT	22,738	3,602	15,677	29,798	9,000	2,168	4,751	13,249

The difference is significant: **p=0,001** (log-rank test)

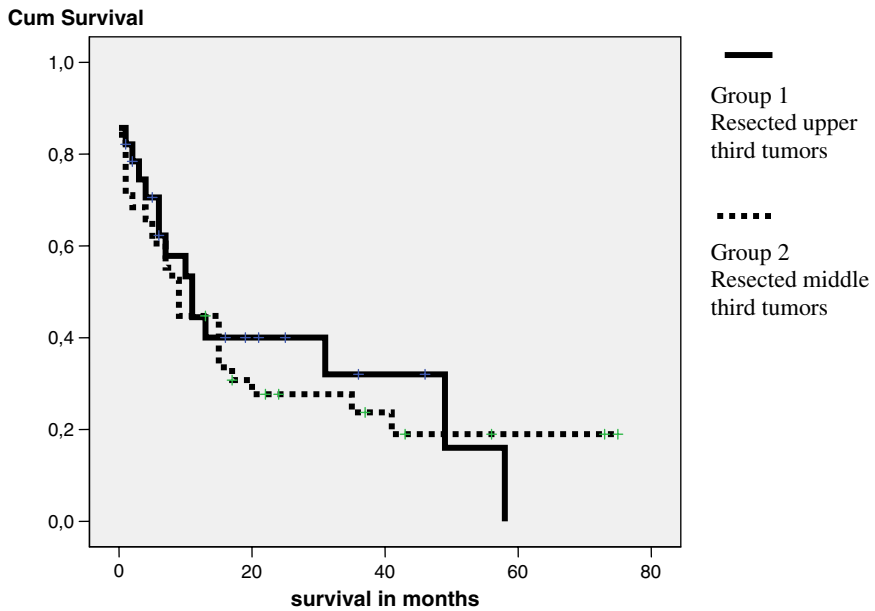


Fig. 3 According to the location, the mean and median survival rate was similar in Group 1 and Group 2.

	Mean(a)				Median			
	Estimate	Std. Error	95% C I		Estimate	Std. Error	95% C Interval	
Location			Lower	Upper			Lower	Upper
Group 1	22,809	4,923	13,160	32,459	11,000	3,038	5,046	16,954
Group 2	22,176	4,692	12,979	31,373	9,000	1,533	5,996	12,004

Difference was not significance: **p=0,724** (log-rank test)

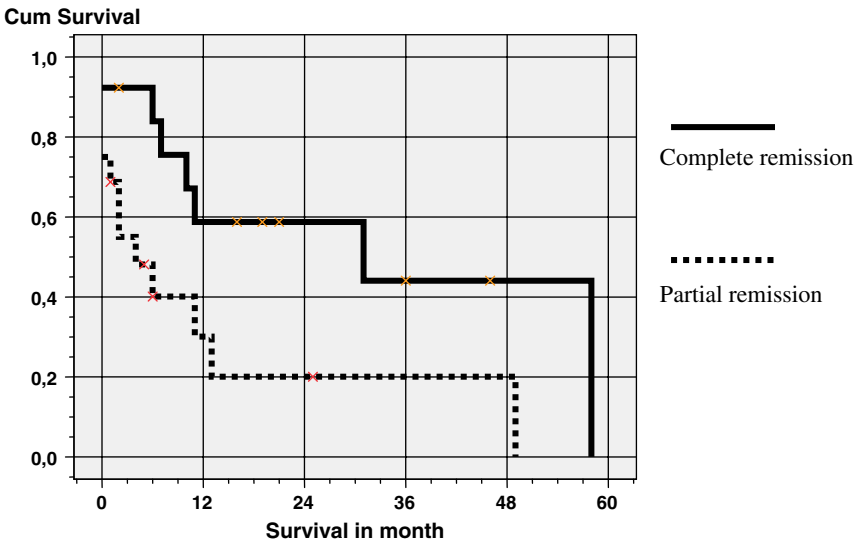


Fig. 4 Survival analysis showed significantly better survival after complete remission

	Mean(a)				Median			
	Estimate	Std. Error	95% C I		Estimate	Std. Error	95% C Interval	
Remission			Lower	Upper			Lower	Upper
Complete	32,958	7,761	17,746	48,170	31,000	22,585	,000	75,267
Partial	13,326	5,478	2,589	24,063	4,000	3,450	,000	10,762

The difference is significant: p=0,024 (log-rank test)

can invade the neighbouring organs early, which especially in the cervical and upper thoracic part results in irresectability, or in need for an extremely extended resection. Anatomical position of the oesophagus causes further problems in the curative treatment. Namely, it is more difficult to perform a correct lymphadenectomy in case of an upper-third oesophageal cancer compared to a lower third tumor (below the level of the azygos vein) and the complications are also higher. This seems to be a feasible explanation for the worse prognosis of the cranially located oesophageal cancer.

A Cochrane Review reported in 2003 [10] that the combination of chemo- and radiotherapy has superior effect in the treatment of oesophageal cancer in an advanced stage over radiotherapy alone. The great advantage of combined preoperative treatment over the adjuvant therapy is, that in neoadjuvant therapy the two different treatment modalities synergicly increase each others effects on cancer in an enviroment with unharmed lymphatic circulation and blood supply. In our study we could also prove this increased survival rate, when comparing recently treated patients to a historical control group (Fig. 1). Recently we know more meta-analyses, which were able to proof that the multimodal treatment of oesophageal cancer improves the survival [16–19]. All meta-analyses have consisted of randomised prospective studies with patients receiving neoadjuvant chemo-radiotherapy before surgery. However it is essential to appoint, that all studies agree to the efficiency of the neoadjuvant therapy, and that significant improvement in the long time survival is only expected, if patients have pCR which occurs in 20–30% [20, 21]. Our results have also confirmed this conclusion (Fig. 4).

However due to flawed methodology in many of the studies results are not fully conclusive [11]. One possible explanation for these contradictory data is that the multimodal therapy—similarly to our experience—increases the perioperative mortality rate to about 15% [12–15] and this unfavorable effect of neoadjuvant therapy decreases the overall survival, aside from some obviously brilliant results of skilled centers [1, 3, 4]. The other problem is that these studies include patients with different tumor types (adenocarcinoma and squamous cell carcinoma) although the different biological behavior and prognosis of these two cancers had already been proven earlier [3]. In our study only patients with locally advanced squamous cell oesophageal cancer were included, which can provide us more accurate information on the effect of neoadjuvant therapy.

In the treatment of oesophageal cancer the upper third tumors (hypopharynx and cervical oesophagus) represent a critical localization, because a neoplasm in a less advanced stage usually requires more extensive surgery [22, 23]. This is one view why this group of oesophageal cancer patients can benefit the most from the multimodal treatment. During our investigation significantly more pCRs were observed in patients with cancer located above the thoracic outlet (Group 1) compared to the mid third tumours (Group 2). Since pCR results in statistically proven survival benefit

(Fig. 4), the higher location does not necessarily mean a disadvantage in the overall survival any more (Fig. 3). It could also mean that multimodal therapy may also be indicated in a less advanced stage.

We can only speculate what the reason for the different response between the two positions is. One reason can be the blood supply. On the better vascularized tissue the chemoradiotherapy is more effective. The blood supply of the intrathoracic oesophagus comes mainly from one or two small vessels from the aorta while the proximal section of the esophagus is well vascularized by large branches from the superior and inferior thyroid arteries [24].

Recently some new randomized studies were published, where chemoradiation with curative intent was compared to multimodal therapy (chemoradiation plus surgery). Based on these results they have concluded that surgery may play a role in the salvage treatment of patients who were defined non-responders to induction therapy, but in patients, who were defined as responders, surgery can no longer be recommended as a routine treatment [25, 26]. A similar study was published in 2000 by Burmeister, who treated a series of 34 patients with carcinoma of the cervical esophagus using chemo-radiation therapy without surgery [27]. Together with other authors they believe that patients with stage II-IV carcinoma of the hypopharynx-cervical oesophagus should undergo primary chemoradiation therapy and should then be carefully re-evaluated by panendoscopy with multiple biopsies and imaging studies (spiral computed tomography, magnetic resonance imaging, positron emission tomography). If there is no evidence of residual disease or stricture at the pharyngo-esophageal junction, the patient can be strictly followed and surgery avoided [23]. These above-mentioned opinions are arguable for more reasons. Based on more trials it is widely accepted that only patients with pCR have longer survival. Furthermore, the surgical resection is currently the only method to document the complete response to neoadjuvant therapy. In our series at upper third tumours a higher rate of complete response (50% in the resected cases) was observed. Their survival was significantly better and possibly due to the effect of the multimodal therapy an organ-preserving surgery could be performed. On the basis of these results we believe that in case of pCR surgical treatment can still be advised, thus the group with the best survival chance will receive the highest level of local tumor control.

Conclusion

In the greater part of the world oesophageal adenocarcinoma exceed the number of squamous cell cancer. The two different tumor types should be analyzed and reported separately to provide comparable results in the future, hence we limited our study to only locally advanced squamocellular oesophageal cancer. In accordance to the data in the literature, our study has also showed that preoperative chemo-radiotherapy improved the survival of patients with locally advanced squamous cell cancer. Patients with pCR after neoadjuvant therapy had significantly better survival compared to all the others. Comparing tumors located to the upper and middle part of the oesophagus a superior sensitivity to the multimodal therapy was observed in the upper third tumors, which is based on the detected higher rate of pCR. It means, that in the era of neoadjuvant chemo-radiotherapy the upper third oesophageal cancer is not the worst location any more.

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