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Neoadjuvant Chemotherapy: Does It Have Benefits for the Surgeon in the Treatment of Advanced Squamous Cell Cancer of the Oral Cavity?

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Abstract The purpose of this clinicopathological study was to evaluate the effects and efficiency of combined neoadjuvant chemotherapy related to surgical margin. 100 consecutively treated squamous cell cancer patients receiving a combined neoadjuvant therapy were selected (Bleomycin—Vincristin—Methotrexate (BVM) or BVM + Mitolactol or BVM + Cisplatin). After three courses of chemotherapy, the patients were operated on. The largest diameter of the primary tumors was compared before and after chemotherapy. In the surgical specimen, the involvement of surgical margin was assessed. The largest diameter before chemotherapy was: T2 30%; T3 55%; T4A 15%. After chemotherapy, the rest tumor was assessed in the surgical specimen as: no rest 11%; <2 cm 57%; 2–4 cm 28%; 4–6 cm 4%. The no rest and <2 cm (optimal operability) tumor was observed in T2: 94%; in T3: 73%; in the T4A: 0%. Severe side effects (Grade III–IV) were not observed. There was a significant decrease in size ($P<$ 0.0001). Of the 100 surgical specimens, 83% had clear-, 9% close- and 8% involved margins. From T4A, there was a 40% (6 patients) involved margin. Based on the significantly better size and operability of primary T2-3, the mild side effects and the high (83%) percentage of clear surgical margins, that is better than other (without preoperative chemotherapy) results, sought the use of chemotherapy is recommended before surgery. Due to the 40% involved margin, we don't suggest surgery in T4A.

Keywords OSCC · Neoadjuvant chemotherapy · Surgical margin · Primary tumor regression · Oral cancer

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Introduction

The morbidity and mortality rates of the oral- and oropharyngeal squamous cell cancer are the most dynamically growing among all malignances which ranks Hungary the first among European countries [1]. The mortality rate increased nearly six fold from 1948 to 2000 and has become a public health problem [2]. This may be caused by the low *Karnofsky* status, the bad habits of patients, and the advanced stage of the disease at presentation. In the last few decades, aggressive and combined treatments were used such as chemoradiation, radical surgery, neoadjuvant chemotherapy etc. [3]. Despite of the considerable advances in the diagnostic and therapeutic possibilities, the prognosis of oral cavity squamous cell cancer remained poor. For successful treatment, cooperation of several specialists is needed [4–6]. Survival depends on the site and stage of the primary tumor, the histological grade and pattern of invasion (biological agressivity), status of the resection

margins, as well as the pathological TNM stage [2, 7, 8]. One of the biggest problems is the primary recurrence after surgical resection in cases of T2–T4A. Despite the use of resection and postoperative radiotherapy, high-risk squamous cell carcinoma of the head and neck frequently recurs in the original bed [9]. *Loree* [10] and *Sutton* [11] detected more than 20% of primary recurrences. These data were even higher, when the surgical margin was involved (36%; 55%), even if the margin was clear (after ablastic resection) the recurrence rate were 18% and 12%. The percentage of patients having close or positive margins progressively increased with increasing T stage. After insufficient resection, the use of adjuvant chemotherapy is not unanimous. *Loree* detected the relative ineffectiveness of adjuvant postoperative radiotherapy in patients with positive surgical margins [10]. In Sutton's study [11], the close or involved cases were irradiated postoperatively and the local recurrence rate was very high (33%; 55%). *Beitler* detected an effective postoperative brachytherapy, but the patient's number [29] was low [12]. *Cooper* found that postoperative chemo- and radiotherapy improved the rates of local and regional control as well as disease free survival in high-risk patients [9]. *Jacobs* showed that the addition of chemotherapy did not significantly alter the median survival of the positive margin patients [13]. The effectiveness of postoperative treatment is uncertain.

May a preoperative setting avoid or decrease this problem?

May it be beneficial for the surgeon in neoadjuvant chemotherapy?

In this clinicopathological study, the quantitative result of chemotherapy induced primary regression and involved surgical margin were investigated.

Patients and Methods

During a 7 year period, 100 consecutively treated patients were entered into this clinicopathological study. Twenty patients received a combination of *Bleomycin—Vincristin—Methotrexate* (BVM), twenty patients received BVM + *Cisplatine*, and 60 patients received BVM + *Mitolactol* (*dibromodulcitol*). The pre-treatment evaluation included history, clinical examination, pan-endoscopy, haematological evaluation, biopsy of the primary and chest X-ray examination. When the stage, resectability or no-resectability was questioned, computed tomography (CT) scans of the chest and head-neck area were obtained. Eligible patients had T2: 30%; T3: 55%; T4A: 15% (AJCC 2002) squamous cell cancer of the oral and oropharynx with no history of previous malignant disease and no distant metastases. *Karnofsky* performance status had to be over 70. Cardiac, hepatic and renal functions were to be within normal limits, leukocyte count greater than 4,000/μl and platelet count over 100,000/μl. Patients were informed about possible treatment modalities and consented to the planned treatment protocol before chemotherapy. Among the 100 treated patients 87 were smokers. The mean age (+/− SD) was 52.4 (+/− 9.7) and 85 were male. The percent in the localization of tumors were as follows: floor of mouth 39, tongue 29, gingiva 20, retromolar trigonum 6, palate 4, bucca 2. In 37 patients CT, in nine patients MRI supported the preoperative assessment of the tumor size. In the rest of the cases the tumor localization allowed measurements on the surface. When the tumor was found on the surface and well identified clinically with inspection and palpation there was not used any CT scan. This clinical method is not as exact as CT or MRI scan (may be a few millimeters difference), but the T stage is tolerable for this few millimeters. (i.e. T2: 20–40 mm etc.) In the surgical specimens T range format were used similarly, rather than exact millimeter formations (see Fig. 1).

Treatment Chemotherapy protocols can be seen on Table 1. Patients received three courses of chemotherapy. After chemotherapy and side effects detection the surgical treatment included resection of the primary tumor and lymph node dissection. Pre-chemotherapy disease extension was used to delineate resection margins.

For the surgical specimen, the standard formalin-paraffin blocks were used in histopathological preparation. Hematoxyline-eosin sections were prepared. The largest diameter of rest tumor was compared in the surgical specimen to the pre-treatment clinical size of the primary lesion (histological quantitative response). The status of the surgical margin was also observed. For the purpose of this study the following definitions were used, as suggested by *Batsakis* [14].

Clear Margin	no evidence of within 5 mm of the margin
Close Margin	within 5 mm of margin
Involved margin	intralesional resection.

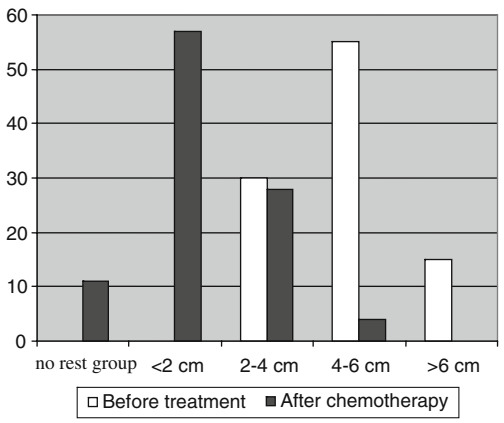

Fig. 1 Distribution of size before treatment and after chemotherapy (%)

Table 1 Chemotherapy protocols

Day	Group N	Group A	
		Group A/C	Group A/M
1. and		2×4 mg/m^2 Bleomycin	
2.		i.m. inj.in per day	
3.	1.5 mg/m^2 Vincristine i.v. inf.		
4.	60 mg/m^2 Methotrexate i.v. inf.	30 mg/m^2 Cisplatin i.v. inf.	400 mg/m^2 Mitolactol per os
5.	7 mg/m^2 Ca-Leucovorine i.m. inj.	60 mg/m^2 Methotrexate i.v. inf.	400 mg/m^2 Mitolactol per os zero time and 60 mg/m^2 Methotrexate i.v. inf. 6 h later
6.		7 mg/m^2 Ca-Leucovorine i.m. inj.	

In the second course of therapy, on the following week the dosages of vincristine, methotrexate and cisplatin or mitolactol (dibromutolcitol) were raised (25%, 100%, 50% and 50%, respectively)

The third course of chemotherapy was administered after a 2-week interval and contained the increased dosage of drugs. Surgery was performed within 3 weeks after the end of the protocol

During cisplatin administration our patients were hydrated and dehydrated and received Zofran to counter the emetic effect of cisplatin

Statistical Method

The existence of any effect of chemotherapy on the tumor size was demonstrated by the Mann-Whitney test. It produced a convincing result of $p<0.0001$ for each initial tumor size groups (T_2, T_3 and T_4) and for the complete sample of 100 cases, too.

The relative change of tumor volume (i.e. tumor bulk) was estimated as follows:

1. The longitudinal size of tumor was estimated by the mean size in the classes of T_1–T_3: 1 cm for T_1 (<2 cm), 3 cm for T_2 (2–4 cm), 5 cm for T_3 (4–6 cm). For class T_4 (>6 cm) the estimate was 7 cm.
2. The volume of tumor was supposed to be proportional with the cube of longitudinal size. E.g. for a tumor of size T_3 the volume was estimated as $\alpha \bullet 5^3$ (α is an unknown, but constant value for all size classes).
3. The individual tumor volumes for a sample were summed up before and after the treatment.
4. The total volume after the treatment was divided by the total volume before the treatment (this step eliminates α).

Results

The side effects of chemotherapy were slight and reversible. Alopecia (Grade I–II.) was observed in 33%. Grade I dermatitis was noted in 2% and 6% had Grade I–II gastritis. Grade I–II mucositis developed in 18% and 7% was Grade II nausea. 28% of the patients developed Grade I anemia and 20% leucopenia. After primary surgery, there was no delayed wound healing.

There was a statistical difference in size before and after chemotherapy (histological quantitative response) ($P<0.0001$).

Before the treatment, the size was 2–4 cm (T2) in 30%, 4–6 cm in 55% (T3) and >6 cm (T4A) in 15% of the cases. After chemotherapy, there was not rest in the surgical specimen 11%; minimal rest (<2 cm) was 57%, 2–4 cm 28% and 4–6 cm 4% (Fig. 1).

No rest and <2 cm was observed in T2: 94%; in T3: 73%; in T4A: 0% (Table 2). The tumor regression in the largest diameter and the tumor bulk reduction in different T stages are shown on Fig. 2.

The resection margin status was clear in 83%, close in 9% and involved in 8% of the cases (Table 3). The numbers of close and involved surgical margins were low. Six involved margins were in the study from T4A (40%) tumors.

Discussion

The number of oral- and oropharyngeal localization ranks Hungary among the first in the European countries [1]. In spite of the different therapeutic modalities, the survival rate remained disappointing in locally advanced OSCC [3, 15–18]. Among the treatments used, the surgical procedure

Table 2 The measure of regression in different T stages

	No rest	<2cm	2–4cm	4–6cm	
T2	24%	70%	6%	–	100%
T3	8.3%	64%	25%	2.7%	100%
T4A	–	–	75%	25%	100%

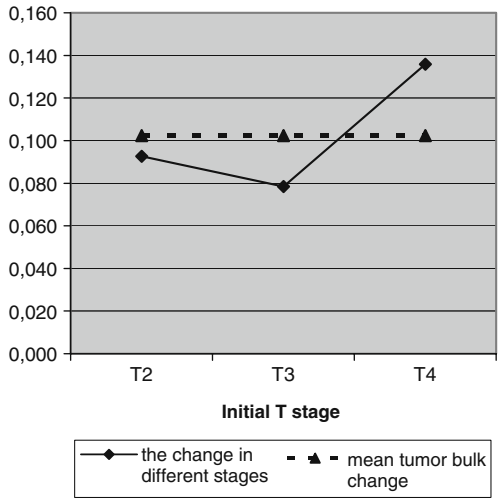

Fig. 2 The change of tumor bulk. The tumor bulk after/before chemotherapy

is one of the most important. The aim of this study was to investigate the surgical benefits of the neoadjuvant chemotherapy in primary OSCC. The surgeon aims at the adequate ablation and to achieve it, a rim of clinically (histologically) normal tissue is resected with the tumor. The inadequate resection leaves the patient with an increased likelihood of disease recurrence and a poorer chance of survival, so the involved margin is a very important prognostic factor [8, 10, 15, 19]. *Sutton* observed significantly greater risk of developing local recurrence in involved (55%) than clear margin (12%) [11]. This difference would be higher as every involved margin patients received postoperative radiotherapy (60 Gy) but not a clear margin. In the study, authors observed a correlation between size and clear or involved margins. When the primary tumor size was less than 20 mm, the clear margin was 81%, but when it was larger than 60 mm this was only 22%. These data show that the local recurrence depends on the clear margin and on the size of primary tumor. In another study, there was a similar significant difference found between early or advanced stages [10].

It is evident that tumor-free or overall survival chances are poorer in advanced than early stages.

What may be a help a surgeon preoperatively to avoid the unsuccessful resection?

Radiotherapy is a widely used treatment in OSCC although its effectiveness is slow, so high doses have to be indicated (60–70 Gy). Only a few studies could be previously found about radical radiotherapy + surgery [20–22]. In these cases, some disadvantages could be observed: adverse conditions in the operation field, inflammation and necrosis of the soft tissue and bone, the high risk of primary recurrence (the rest cannot be exactly identified in the irradiated field), etc. As a result, limited doses (30–40 Gy) with or without chemotherapy (chemoradiation) are suggested preoperatively [23] these days.

The appreciation of neoadjuvant chemotherapy is uncertain in different studies. *Licitra*, *Volling*, *Jacobs* demonstrated no significant difference in disease-free or overall survival, but *Licitra* observed less mandibulectomy and/or radiation therapy in the chemotherapy arm [16, 24, 25]. *Maipang* did not observe improving overall survival, but the chemotherapy responders, however, did better than non-responders [26]. *Olasz* compared preoperative radiotherapy with chemotherapy and observed no statistical difference in the 3-year overall survival, but the local recurrence rate was significantly better in the chemotherapy arm [27]. *Kovács* suggests the use of neoadjuvant chemotherapy for the treatment of all stages of primary oral cavity SCC [28]. Similar experiences can be seen in chemoradiation. *Al Sarraf* observed better 5-year overall survival with chemoradiation than radiotherapy alone [29].

Benasso observed significantly better overall survival in the chemotherapy + radiotherapy group than radiotheapy alone at the coordinating centre, but in the affiliated centre no difference was detected [30]. *Hironaka* compared chemoradiation to surgery in operable esophagus SCC. The 5-year survival results detected no statistical difference, but the TNM stage was more advanced in chemoradiation [31]. *Psyrri* observed that the induction chemotherapy (cisplatin + fluorouracil + leucovorine) followed by concurrent cisplatin chemoradiotherapy is well tolerated, and results in a good likelihood of organ preservation and excellent progression free and overall survival chances [32]. Thanks to the work of *Forastiere* chemoradiotherapy has become the standard care for the nonoperative management of locally advanced oropharyngeal cancer [5, 33].

The effectiveness of chemotherapy against SCC can be seen in different studies [28, 34–36]. The response rates are between 70–90%. The most effective and frequently used drugs are cisplatin and 5-Fu [9, 37–39]. These studies show high clinical complete and partial responses, but usually are not highly informative for surgeons.

In the investigation of induction chemotherapy, pathologic evaluation and results are more exact and revealing than clinical responses [35, 40]. Pathologically qualitative and quantitative responses can be observed. Among the qualitative ones, inflammatory reactions (chronic lymphocytic and giant cell granulomatosus type), scar formation and/or myofibroblastic reaction, the histology type, necrosis

Table 3 The surgical margin status in different studies

	Olasz	Sutton[11]	Woolgar[46]	Loree[10]
Clear	83	53,5	35	68
Close	9	42	50	
Involved	8	4,5	15	32

and grade of tumors, and involved margin are usually evaluated, as some studies prove [40–43]. Both clinical and pathological results together may be informative about the efficiency of preoperative chemotherapy [44, 45].

An earlier study showed the possible benefit of bleomycin, vincristine, mitolactol and methotrexate (BVMM) induction chemotherapy in stage II–IVa oral-oropharyngeal cancers. Due to the merger of the manufacturer, production of mitolactol had stopped and we changed to another effective widely used anti-cancer platin containing regimens. To compare the new BVCM with our earlier results, we developed a randomized prospective study, comparing cisplatin and BVM to a simplier standard (BVM) chemotherapy combination. According to our former conclusion there was no significant difference among clinical responses [35, 43].

In this study, the post-chemotherapy size was significantly smaller than the one before the treatment. In T2 tumor 94%, in T3 tumor 73%, while in T4A 0% became no rest or minimal (<2 cm) rest (optimal operability) in the surgical specimen (Table 2). From these results it can be seen that as far as the size is concerned, the neoadjuvant chemotherapy may result a successful resection except for the very advanced T4A-s. In T4A primary cases, the unfavorable long survival is evident, because of the high percentage of involved resection margin [10, 11]. In this study involved resection margin in T4A was 40%.

Does resection margin status benefit from preoperative chemotherapy?

Sutton 53,5%, *Woolgar* 35% observed clear margin, but in this study this was 83% [11, 46]. The difference came from the close margin: while in the above mentioned studies it was approximately 50%, in this study it was only 9%. Moreover, initial tumor size was more unfavorable in this study (70%) than in *Sutton's* (45%) or *Woolgar's* (59%) paper. The post-chemotherapy histological picture may explain the difference, where, as it was published earlier, in many cases, a fibrous scar may separate the rest tumor from the healthy tissues [27, 35, 40, 41, 43].

Though the tumor bulk regression is higher in T4A than T2, this does not mean safer operability (high involved surgical margin). It may be caused by the large necrotic state, the usually bad general condition, and an insufficient immune reaction. Although T4A stage is an operable stage (AJCC 2002), we do not suggest operation for T4A stage.

Conclusion

Operating on a primary tumor, the benefits of neoadjuvant chemotherapy for a head neck surgeon are:

- significant regression
- favorable operability (demarcation)
- higher rate of clear margin

Conflict of interest and funding source All authors state that there are no financial interests or commercial associations that may create a conflict of interest with information presented in this manuscript.

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