

## **I. Introduction**

Therapy of head and neck cancer depends primarily on the clinical tumour stage at the time of the first diagnosis. The early stage cancers can successfully be treated either by surgery or radiotherapy, whereas each of the advanced ones requires a so called multimodal oncotherapy, provided that the patient's general state permits it.

From the '90<sup>ies</sup>, several clinical studies with the aim of organ sparing and function preservation proved that without jeopardizing local control and overall survival the advanced head and neck cancer could be treated with primary chemoradiotherapy instead of radical surgery.

After these results manifested in the clinical routine the survival of patients treated for laryngeal cancer in the USA deteriorated. Searching for the possible factors in the background of these results directed the attention to the comorbidities of the cancer patient. Since head and neck cancer is mostly caused by environmental factors, such as alcohol consumption and smoking, and both can induce several non-cancerous diseases, primarily pulmonary and cardiovascular ones, nearly one quarter of head and neck cancer patients suffer from moderate or severe comorbidities.

Although these findings could explain the differences between the results of clinical trials and the treatments in the clinical routine, the studies failed to include comorbid patients into the study population.

In our retrospective study we investigated the possible correlation of comorbidity with the completeness of the chemoradiotherapy, clinical tumour stage and survival among advanced head and neck cancer patients.

## **II. Objectives**

1. Evaluation of survival of patients with advanced head and neck tumours in different anatomical localizations and stages after primary and postoperative chemoradiotherapy.
2. Does the comorbidity value measured before starting chemoradiotherapy in advanced head and neck tumours correlate with the complete delivery of the treatment and with survival?
3. How do the surgical and non surgical treatment results of previously untreated, advanced, operable laryngeal and hypopharyngeal cancers compare with one another in the National Institute of Oncology?

## **III. Study population and methods**

We evaluated the data of 359 chemoradiotherapies delivered for advanced head and neck squamous cell cancers in the National Institute of Oncology, Budapest from 1<sup>st</sup> January 2001 to 31<sup>st</sup> December 2007. We collected data from the patient's gender and age at the beginning of the treatment, comorbidity factors on the basis of ACE-27 scale, histological type and grade as given in the histology report, the anatomical localization of the tumour, results of imaging exams, tumour stage according to the TNM classification, previous tumour related treatments, if any, type of therapy(ies) delivered in our Institute, including dose and duration, and the fact whether the treatment was completed according to the treatment plan, the dates and results of control examinations, and the time when the recurrence appeared, if any, further treatments for the recurrence, and the actual state of the patient.

The similar the data of patients, undergone laryngectomy for advanced, but operable stages III and IVa laryngeal and hypopharyngeal cancer during the same study period, were also processed together with their follow up data.

## IV. Results

### 1. Chemoradiotherapies

Assessing correlations of the variables with the  $\chi^2$  test in the whole sample and then separately in the subgroup of patients receiving primary chemoradiotherapy showed correlation at the highest level of significance between the comorbidity and the completeness of the treatment, as well as between the comorbidity and the life and death variable. Astonishingly, there was no connection between the comorbidity and the tumour stage. The *correlation matrix* represents the connection of the individual variables. In harmony with the  $\chi^2$  test, these results confirmed that the completeness of the treatment is subject, first and the foremost, to comorbidity, their correlation coefficient was strikingly high: 0,4953, strongly significant.

By means of the *discriminance analysis* we tried to identify the independent prognostic factors. We have seen that the survival of the patient is predominantly determined by the completeness of the treatment, which is strongly correlated with comorbidity measured by ACE-27 scale. Congruently, with the *Cox regression analysis* we could indentify that the strongest prognostic factors of survival are, in the whole sample and in the group of patients given primary treatment, the comorbidity and completeness of the treatment, stronger, than the tumour stage in itself.

### 2. Comparison of surgical and non-surgical treatments in laryngeal and hypopharyngeal cancers of Stage III and Stage IV

The median overall survival of patients receiving chemoradiotherapy for stage III and IV hypopharyngeal cancer was not significantly different from the patients undergone primary laryngectomy.

## V. Conclusions

One cannot turn back time. By now in case of head and neck cancer both the patient and the attending physician, be him either a head and neck surgeon, or a radiotherapist, naturally endeavour to the preservation or reconstruction of function when choosing the actual treatment modality. With some of the therapies these aims can be reached by special surgical techniques. However, in some other cases, for instance in advanced cancers of the larynx, hypopharynx or just of the tongue, the missing organ cannot be reconstructed; its loss irreversibly ruins the patient's quality of life. In such cases the guidelines recommend the cisplatin based concomitant radiochemotherapy as a function preserving treatment modality. They may do so because several clinical studies and meta-analyses have proven that this treatment modality is able to realize the aims of function preservation without jeopardizing local control and survival. Our retrospective study and review of relevant literature were inspired by the observation that in a certain proportion of patients treated in routine clinical setting one fails to reproduce the survival rates after radical surgery, or non-surgical therapy in the clinical studies.

1. Our literature survey has shown that compared to a real patient population of a clinic, the clinical studies which serve as a basis for guideline recommendations – in the present case recommending chemoradiotherapy as an optional non-surgical treatment modality – work

with considerable selection bias. First of all patients with multiple coexisting diseases are under-represented in the samples of the clinical studies.

2. In our study population consisted of 359 patients the results of chemoradiotherapy have shown that primarily the moderately and severely comorbid patients are those to whom complete chemoradiotherapy cannot be delivered.

3. It was also demonstrated that the survival of patients given incomplete treatment was definitely inferior to the expected survival. Therefore, it can be stated that the benefits of the burdensome and aggressive chemoradiotherapy and finally, the function preservation, become real only with patients in good general condition, and with no, or only mild comorbidity, after complete treatment.

4. Publications and recommendations are sparse in the literature regarding treatments developed for comorbid patients who are probably not candidates for complete chemoradiotherapy. The alternative treatment modality includes radical surgery complemented, if necessary, with postoperative radiotherapy or with low dose chemoradiotherapy. To the best of our knowledge, no article has been published on the results of radiotherapy in itself in comorbid patients. They are supposed to be inferior to those attainable by chemoradiotherapy. On the other hand, it can also be presumed that a total dose radiotherapy would surpass the effectiveness of chemoradiotherapy interrupted for side effects. A comparative study on this issue might yield essential pieces of information.

5. The therapy of all cancer patients requires a concerted action by the representatives of different specialties. Accordingly, the therapy of head and neck cancer patients in the National Institute of Oncology, Budapest is based on the proposals of a multidisciplinary onco-team. These therapeutic decisions were also analysed retrospectively in resectable pharyngeal and laryngeal cancers based on the results of 44 chemoradiotherapies and 207 surgeries. In this population the survival data of patients given organ and function preserving treatments were not less favourable than those attainable by surgery and they are comparable with international data.

## **V.1 New results**

1. We proved that in the clinical studies that have brought about a change of paradigm in the therapy of patients with advanced head and neck cancers, the rather high proportion of patients with multiple coexisting diseases in all cancer patient populations was under-represented in the samples.

2. We could establish strong correlation between the comorbidity of head and neck cancer patients and the completeness of their chemoradiotherapy as specified in the treatment protocol and overall survival, respectively.

3. Since opposite to surgery, the effectiveness of chemoradiotherapy is strongly dose-dependent, the proposal of the multidisciplinary onco-team for the actual treatment modality is crucial, particularly in the case of resectable tumour and operable patient. We could prove, that in contrast to the data registered in USA, the results of the primary surgical and non-surgical treatments for locally advanced resectable laryngeal and hypopharyngeal cancers in the National Institute of Oncology, Budapest from 2001 to 2007 do not differ from one another and are in harmony with the results of the international studies.

## **VI. Publications**

1. **Koltai P**, Remenár E, Boér A, Fülöp M, Koltai L, Oberna F, Udvaros I, Pólus K, Kásler M.: Neoadjuváns kemoterápia fej-nyaki laphámrákban. *Magy Onkol.* 2001;45(2):197-199.

2. **Koltai P**, Hegyesi H, Molnár V, Óvári A, Péter I, Falus A, Kásler M.: Coexpression of c-kit and stem cell factor in head and neck cancer. *Revista de Medicină și Farmacie - Orvosi és Gyógyszerészeti Szemle*, 2009, 55: 215-221

3. **Koltai P**, Lengyel Cs, Remenár É, Boér A, Kásler M.: Primary Surgical and Non-surgical Treatment of Advanced Stage Laryngeal and Hypopharyngeal Carcinomas. *Acta Medica Marisiensis* 2012, 58(2): 102-105