

Primary Surgical and Non-surgical Treatment of Advanced Stage Laryngeal and Hypopharyngeal Carcinomas

Koltai P, Lengyel Cs, Remenár Éva, Boér A, Kásler M

Department of Head and Neck Surgery, National Institute of Oncology, Budapest, Hungary

In the past two decades, according to studies published in the early '90s, the standard treatment of advanced laryngeal and hypopharyngeal carcinomas has been changed: instead of radical surgery, larynx-preserving methods came into view. To evaluate our results with this new approach we conducted a retrospective study summarizing the treatment data of the patients who received non-surgical (n=44) or surgical (n=207) therapy for their advanced, resectable laryngeal or hypopharyngeal cancer in the National Institute of Oncology between 2002 and 2007. Non-surgical treatment consisted of platinum base chemoradiotherapy plus salvage surgery if needed, while surgical treatment patients underwent laryngectomy with or without neck dissection followed by radiotherapy or chemoradiotherapy. With non-surgical treatment, the one-year laryngoesophageal dysfunction (LED) free survival (the patient is alive with functioning larynx without local relapse, tracheostomy or feeding tube) is 82.9% (SD=0.0592), at 24 months 79.8% (SD=0.0645). Non-surgical treatment proved to be beneficial regarding distant metastases as well (9.09% in non-surgical and 27.08% in surgical group at two years, respectively). Formation of a second primary tumor was more frequent in the non-surgical group (11.36% vs 8.33%). There was no significant difference in overall survival between treatment groups when stratified according to primary tumor site and stage. The results of larynx preserving treatments conducted in our Institute are similar to those published in the literature, confirming this method as standard therapy in this group of patients.

Keywords: head and neck cancer, laryngectomy, chemoradiotherapy, larynx preservation

Received: 16 April 2011 / Accepted: 16 June 2011

Introduction

Head and neck cancers represent nearly 5% of all cancers, with an estimated worldwide incidence of around 650,000, causing 350,000 deaths in a year. In Hungary cancer of the oral cavity and the pharynx is the second most common cause of cancer death after lung cancer among 40–60 year-old men. The incidence of the disease in this location increases in Hungary not only in this age group, but also among women and younger men, in spite of the decreasing tendency in the western world. According to the data of Hungarian Cancer Registry, in the past ten years around 700 hypopharyngeal and 1300 laryngeal cancers have been diagnosed constantly each year.

International Classification of Diseases (ICD) codification classifies the carcinomas of lips, oral cavity and pharynx including hypopharynx separately from carcinomas of the larynx, that is encoded as a representative of respiratory tract cancers. Although hypopharyngeal and laryngeal cancers differ in many ways in their origin, anatomical and biological behaviour, from the oncological and surgical point of view it is reasonable to discuss them together.

Till the '90s the traditional therapy of larynx and hypopharynx cancers was radical surgery, in most cases laryngectomy, completed with partial resection of hypo- or mesopharynx, base of the tongue if necessary, followed by postoperative radiotherapy. Function sparing therapy for laryngeal or hypopharyngeal cancer patients was only ap-

plicable in early stage diseases either with radiotherapy or with partial resection of the larynx.

Recognition of the effectiveness of platinum based chemotherapy in head and neck squamous cancer resulted in conduction of trials investigating organ preservation methods in advanced diseases. In the first generation studies, conventional treatment (i.e. laryngectomy followed by radiotherapy) has been compared to larynx preservation treatments, namely induction chemotherapy with cisplatin and 5FU combination, followed by radiotherapy in the responders, and laryngectomy and postoperative irradiation in the non-responders. There were two major studies in this field: one for laryngeal cancer conducted by the Department of Veterans Affairs in the USA [1] and one for hypopharyngeal cancer conducted by EORTC (24891) [2,3] in Europe. According to the results of these trials with the above mentioned approach, in 51–64% of cases larynx preservation can be achieved without compromising survival.

The two most important second generation organ preservation trials (RTOG 91-11 and EORTC 24954) [4,5] aimed to compare different combinations and timing of chemotherapy and irradiation, and resulted in the standard setting of platinum based synchronous chemoradiotherapy used nowadays, as the standard, non-surgical treatment.

Because of the comparative results of primary surgical and organ sparing, non-surgical approaches of treatment, for ethical and organizational reasons, no further prospective randomized studies could be conducted to compare the two modalities directly. It is of utmost importance to evaluate the outcome of these treatments in practice, as

none of them achieve better survival than the other, and both have a negative impact on the quality of life in different ways [6,7].

Method and patients

A retrospective study was designed based on data collection from the head and neck cancer database of the National Institute of Oncology, Budapest and Hungarian National Cancer Registry. Patients included in the study were treated with laryngectomy or with chemoradiotherapy between 2000 and 2007 for laryngeal or hypopharyngeal cancer as primary treatment, and had advanced stage resectable (stage III or IVa) disease without distant metastases. (According to AJCC/UICC staging (UICC – Union International Contre le Cancer, AJCC – American Joint Committee on Cancer)).

For statistical calculations we used MedCalc Statistical Software version. 9.4.2.0., Broekstraat, Belgium. For survival analysis and graphical visualisation of survival curves with used the same software and the Kaplan-Meier method. Survival times were measured from the first diagnosis of the disease.

Chemoradiotherapy consisted of a planned total dose of 70 Gy in 2 Gy fractions daily, delivered over seven weeks to areas of gross disease and high-risk microscopic disease, and 45 Gy to areas of low-risk microscopic disease. Patients received synchronously 3 cycles of cisplatin treatment each in a dose of 100 mg/m² on the 1st, 22nd and 43rd days of treatment. All patients have been simulated prior to radiotherapy, nowadays 3D CT based radiotherapy planning is used in most treatments. Patients underwent CT or MRI of the neck, chest CT, abdominal US, ECG or heart US and laboratory examinations before the treatment. Laboratory examinations have been performed prior and after every cycles of chemotherapy. Ten–twelve weeks after the completion of the therapy, control CT of MRI was performed with the same method like before the treatment. In case of suspicion of any residual disease either on primary tumor site or on the neck, every effort was made to obtain a pathological diagnosis through biopsy (direct biopsy, US or CT guided cytology, core biopsy). In case of pathologically proven or suspected residual disease, further oncotherapy followed, in most cases surgical therapy, according to the decision of the oncoteam. If persistent

enlarged lymph node was detectable on the neck, PET/CT was performed to evaluate the activity of the node. According to the result of the PET/CT and to the size and morphology of the lymph node, neck dissection was possible to carry out without positive cytology as well. No planned dissection was performed in any pretreatment stage, if no pathological lymph nodes were present. Posttherapy surveillance included outpatient evaluation every 3 months by the treating physician, radiological control every 6 months for 3 years, and then according to the decision of the treating physician, further control for at least additional 2 years.

Laryngectomy was performed according to professional rules, with neck dissection in case of suspected or proved metastatic lymph node on the neck. The treatment protocol consisted of 50–70 Gy postoperative irradiation. Indication of postoperative chemoradiotherapy was histopathologically proven lymphovascular or perineural spread, infiltration of the capsule of the lymph node or near surgical margin. Chemoradiotherapy scheme was identical to the one described above.

Results

Between 2000 and 2007, 44 patients (37 males and 7 females, median age at the beginning of treatment 55.8 years) received chemoradiotherapy, 36 (82%) because of hypopharyngeal and 8 (18%) because of laryngeal carcinoma. The laryngeal cancer group consisted of 2 cases (5%) with stage III and 6 cases (13%) with stage IVa disease, whereas among hypopharyngeal cancers there were 11 cases (25%) of stage III and 25 cases (57%) of stage IVa tumors. At the time of diagnosis, 35 patients had detectable metastasis on the neck (79%) of whom 14 (32%) had contralateral or bilateral. The median received dose of radiotherapy was in fact 66 (30–74) Gy.

In the same period, 207 patients underwent laryngectomy (180 males and 27 females, median age at the operation 54 years), 134 of them (64.7%) because of hypopharyngeal and 73 of them (35.3%) of laryngeal carcinoma.

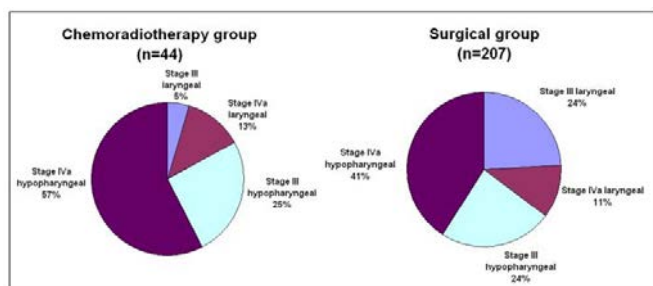


Fig. 1. Distribution of cancer location and stages in the primary chemoradiotherapy and surgical treatment group

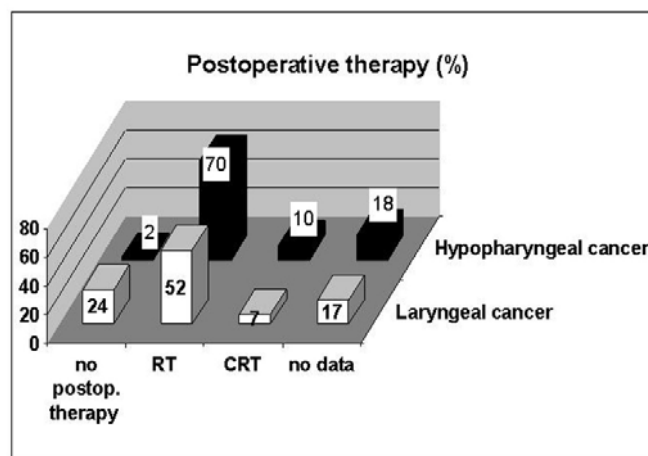


Fig. 2. Percentage of postoperative treatment according to cancer location after radical surgery in surgery group. (RT: radiotherapy, CRT: chemoradiotherapy)

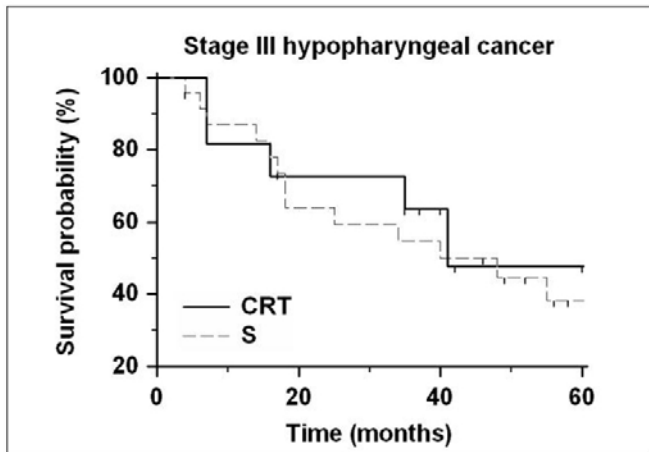


Fig. 3. Kaplan-Meier analysis of survival of stage III hypopharynx cancer patients after primary chemoradiotherapy (CRT) and primary surgical treatment (S)

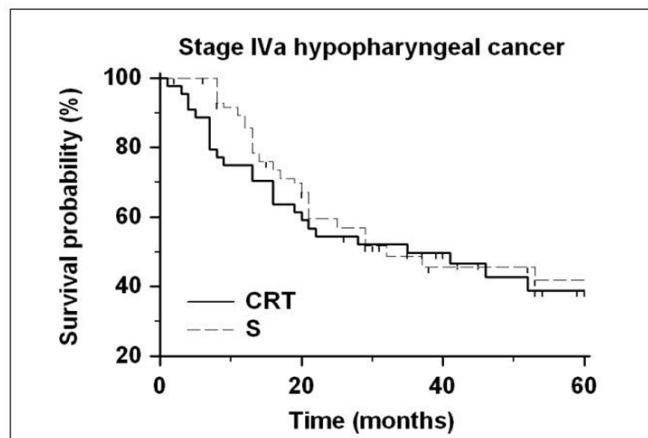


Fig. 4. Kaplan-Meier analysis of survival of stage IVa hypopharynx cancer patients after primary chemoradiotherapy (CRT) and primary surgical treatment (S)

Among laryngeal cancers stage III was observed in 50 cases (24%) and stage IVa in 23 cases (11%), whereas among hypopharyngeal cancers stage III was in 49 cases (24%) and stage IVa in 85 cases (41%) (Figure 1). At 101 laryngectomies simultaneous neck dissection has been performed, three of them were bilateral. In 59% of laryngeal and in 80% of hypopharyngeal cases, postoperative radiotherapy or chemoradiotherapy was undertaken (Figure 2).

Median overall survival of patients with stage III hypopharyngeal cancer treated with chemoradiotherapy was 41 months versus 40 months for those who underwent laryngectomy, the difference is not significant ($p=0.9722$) (Figure 3). Median overall survival is although better in stage IVa hypopharyngeal cancers treated with CRT than treated with surgery (35 vs. 32 months, respectively), the difference is not significant either ($p=0.3454$) (Figure 4).

Laryngoesophageal dysfunction (LED) free survival (the patient is alive with functioning larynx without local relapse, tracheostomy or feeding tube) for the chemoradiotherapy group ($n=44$): at 12 months 82.9% ($SD=0.0592$), at 24 months 79.8% ($SD=0.0645$) (Figure 5).

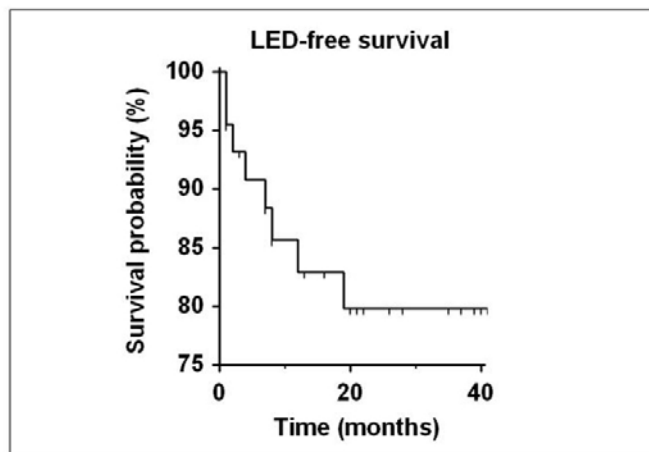


Fig. 5. Laryngoesophageal dysfunction (LED) free survival after primary chemoradiotherapy

The low number of laryngeal cancers in the chemoradiotherapy group (2 stage III and 6 stage IVa) is insufficient for statistical analysis or graphical visualisation of survival curves.

Among patients treated with chemoradiotherapy, 7 (15.9%) needed tracheostomy and in one case we had to perform salvage laryngectomy.

Non-surgical treatment proved to be beneficial respecting distant metastases (9.09% in non-surgical and 27.08% in surgical group at two years, respectively, the difference was not significant). The rates of formation of a second primary tumor in the surgical and non-surgical group was 8.33% and 11.36%, respectively, the difference was not significant either (Figure 6).

Discussion

As laryngectomy affects the patient's quality of life very negatively, since the first attempts of laryngeal and hypopharyngeal cancer treatment ENT surgeons, radiotherapists and oncologists were trying to find the ways for organ

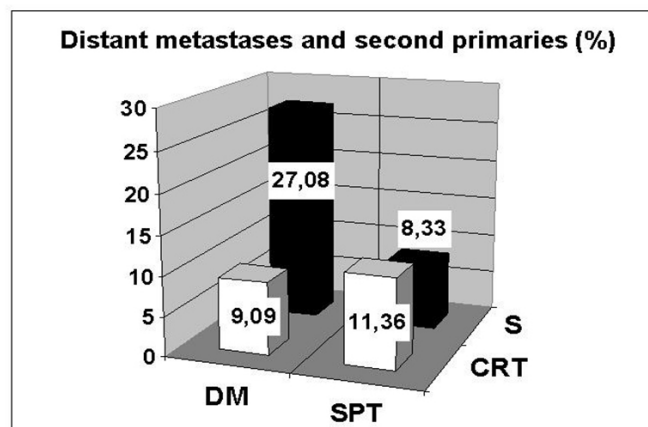


Fig. 6. Percentage of formation of distant metastases and second primary tumors within two years after different forms of primary treatment of laryngeal or hypopharyngeal cancer (S: surgery, CRT: chemoradiotherapy)

preserving therapies. Till the two major trials published in the '90s proving that in about two third of advanced stage diseases larynx preservation can be achieved without compromising survival, only laryngectomy with postoperative radiotherapy was the therapy of choice with curative intent in this group of patients [9–11].

Although pioneer studies focused only on the preservation of the organ, nowadays the expectations put emphasis primarily on functioning [12]. The latest recommendations for treatments and trials have been introduced the category of laryngoesophageal dysfunction (LED) free survival, i.e. the patient is alive with functioning larynx without local relapse, tracheostomy or feeding tube [6]. Considering these, it is contraindicated to preserve the larynx, if it has been irreversibly damaged, signed by swallowing or breathing impairment with the need of tracheotomy or feeding tube or causing pneumonia. Extracartilaginous tumor spread and the age of more than 70 years are also contraindications for organ preservation. Consequently, selecting patients for laryngectomy or organ preserving treatment is a very comprehensive task: characteristics of the tumor, age, social status and co-morbidities of the patient must be taken into consideration [13]. Hungary belongs to those countries in Europe, where laryngeal surgery was the dominant method of choice in laryngeal and hypopharyngeal cancer treatment, even a decade after the success of non-surgical therapies in the USA and in Western Europe. The majority of operated patients compared to chemoradiotherapy cases in this paper also reflect this treatment philosophy.

Despite of these, our results are comparable to the outcome of the trials, in the sense that among those patients who received primary non-surgical treatment we achieved similar overall, laryngectomy free and laryngoesophageal dysfunction free survival rates as it is in the studies. At the time of the treatments evaluated in this paper neither quality of life, nor functional measurements were performed to know more about these aspects of our treatments of either types, and to improve our skills in treatment indication; regular follow-up with validated instruments of quality of life and laryngeal function is necessary.

Conclusions

Our results are comparable to the outcome of the trials. The rate of surgical and non-surgical treatments reflects the complex condition of patients at the time of the therapeutic decision. The team of specialists responsible for the treatment consisting surgeon, radiotherapist, clinical

oncologist, pathologist, radiologist, phoniatrician and psychologist have to take into account the patients whole pathological and psychosocial status to find the best therapy of choice for each individual patient. At the evaluation of the treatment results, one has to consider survival rates, laryngectomy free survival rates and laryngoesophageal dysfunction free survival rates as well. To improve expertise in finding the best therapeutic choice for each patient, besides survival data we have to evaluate quality of life and laryngeal function measurements in ongoing treatments.

References

1. Wolf G, Hong K, Fisher S and The Department of Veterans Affairs Laryngeal Cancer Study Group: Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. *N Engl J Med.* 1991;324(24):1685-90.
2. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahnoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst.* 1996;88(13):890-9.
3. Lefebvre JL, Chevalier D, Luboinski B. Is laryngeal preservation (LP) with induction chemotherapy (ICT) safe in the treatment of hypopharyngeal SCC? Final results of the phase III EORTC 24891 trial. (abstract 5531). *J Clin Oncol* 2004;22(suppl 14):495s.
4. Weber RS, Berkey BA, Forastiere A, Cooper J, Maor M, Goepfert H, Morrison W, Glisson B, Trotti A, Ridge JA, Chao KS, Peters G, Lee DJ, Leaf A, Ensley J. Outcome of salvage total laryngectomy following organ preservation therapy: the Radiation Therapy Oncology Group trial 91-11. *Arch Otolaryngol Head Neck Surg.* 2003;129(1):44-9.
5. Lefebvre JL, Rolland F, Tesselaaar M, Bardet E, Leemans CR, Bernier J, Vermorken JB; EORTC Head and Neck Cancer Cooperative Group; EORTC Radiation Oncology Group. Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. *J Natl Cancer Inst.* 2009;101(3):142-52. Epub 2009 Jan 27.
6. Ang KK. Larynx preservation clinical trial design: summary of key recommendations of a consensus panel. *Oncologist.* 2010;Suppl 3:25-9.
7. Lefebvre JL, Ang KK. Larynx Preservation Consensus Panel: Larynx preservation clinical trial design: key issues and recommendations – a consensus panel summary. *Head Neck.* 2009;31(4):429-41.
8. Yun HJ, Bogaerts J, Awada A, Lacombe D. Clinical trial design limitations in head and neck squamous cell carcinomas. *Curr Opin Oncol.* 2007;19(3):210-5.
9. Hoffman HT, Karnell LH, Funk GF, Robinson RA, Menck HR. The National Cancer Data Base report on cancer of the head and neck. *Arch Otolaryngol Head Neck Surg.* 1998;124(9):951-62.
10. Hoffman HT, Porter K, Karnell LH, Cooper JS, Weber RS, Langer CJ, Ang KK, Gay G, Stewart A, Robinson RA. Laryngeal cancer in the United States: changes in demographics, patterns of care, and survival. *Laryngoscope.* 2006;116(9 Pt 2 Suppl 111):1-13.
11. Hoffman HT, Weber RS, Ang KK, Gay EG, Langer CJ. National Cancer Database report on cancer of the head and neck: 10-year update. *Head Neck* 2009;31(6):748-58.
12. Chen AY, Schrag N, Hao Y, Flanders WD, Kepner J, Stewart A, Ward E. Changes in treatment of advanced laryngeal cancer 1985-2001. *Otolaryngol Head Neck Surg.* 2006;135(6):831-7.
13. Chen AY, Halpern M. Factors predictive of survival in advanced laryngeal cancer. *Arch Otolaryngol Head Neck Surg.* 2007;133(12):1270-6.