THE IMPACT OF THE TIME FACTOR ON THE OUTCOME OF A COMBINED TREATMENT OF PATIENTS WITH LARYNGEAL CANCER

Piotr Milecki[1], Grażyna Stryczyńska[1], Aleksandra Kruk-Zagajewska[2]

Department of Radiotherapy, The Great Poland Cancer Centre, ul. Garbary 15, 61-866 Poznań, Poland[1]
Department of Otolaryngology, The University School of Medical Sciences, ul. Przybyszewskiego 49, Poznań, Poland[2]

Received November 9th, 2001; received in a revised form April 11th, 2002; accepted July 15th, 2002

ABSTRACT

Purpose: To investigate the impact of the time factor on the locoregional control in combined treatment (surgery and postoperative radiotherapy) in patients with advanced laryngeal cancer.

Materials and Methods: Between January 1993 and December 1996, 254 patients with pT3 or pT4 and pN0- pN2 laryngeal cancer were treated by surgery and postoperative radiotherapy (RT). The median age of patients was 56.3 years (range: 30 -70 years). The analyzed group consisted of 236 males (92%) and 18 females (8%). In all cases total laryngectomy was performed. 196 out of 254 patients underwent homolateral neck dissection and 58 out of 254 bilateral neck dissection. RT began 45 days postoperatively (range: 22 to 78 days) and continued for 47 days (range: 40-74 days). The primary tumour bed was irradiated to the median total dose of 61.2 Gy (range: 57 – 64 Gy) and all regional lymph nodes were treated in all patients to a dose of 50 Gy. Postoperative RT was indicated in case of close postoperative margins at the tumour site or pathological status of lymph nodes described as pN1 or pN2. Univariate and multivariate analyses were used to determine the predictors for locoregional failure. The following factors were studied for their prognostic importance of locoregional outcome: the overall treatment time (OTT), radiotherapy treatment time (RTT), the interval between surgery and the beginning of radiotherapy, age, sex, pT and pN categories.

Results: The actuarial 5-year overall survival rate was 49%, the actuarial loco regional control rate was 70%. The univariate analysis, using a log-rank test indicated that prolongation of the overall treatment time (OTT), the time of radiotherapy (RTT), the interval time between surgery and radiotherapy, and the pN status were predicted for the loco regional control of postoperative radiotherapy. The multivariate analysis using Cox proportional hazard model indicated that only RTT, OTT, and the pathological status of lymph nodes were independent prognostic factors for the loco regional control.

Conclusions: The analysis showed that the prolongation of the overall treatment time of the combined modality (OTT) and the time of radiotherapy course (RTT) were independent prognostic time factors correlated with lower loco regional control.

Key words: Laryngeal carcinoma, postoperative radiotherapy, time factor.

INTRODUCTION

In advanced laryngeal cancer, combined treatment consisting of surgery and postoperative radiotherapy is a standard treatment modality in many centers across the world [1,2,3,4,5,6]. Despite the fact that the margins of resection are described as negative, postoperative radiotherapy in head and neck cancer is usually recommended due to the significant relapse rate in T3 or T4 tumours and N1 or N2 or N3 neck disease [7,8].

Numerous data from literature indicate that the protraction of radiotherapy alone or in postoperative modality caused a decrease in local and/or regional outcome of treatment [9,10,11]. The accelerated repopulation of clonogenic tumour cells accounts the negative influence of the time factor [12]. The importance of the total time of combined treatment measured

from surgery (first day) to the end of radiotherapy (the last day of treatment), the time interval between surgery and the beginning of radiotherapy, and the time of radiotherapy in laryngeal cancer has not been as yet precisely determined.

The purpose of this study is to evaluate the effect of the time factor in postoperative radiotherapy, defined as the overall treatment time, the time between surgery and the beginning of radiotherapy, and the time of radiotherapy on the locoregional outcome of combined treatment in advanced laryngeal cancer.

MATERIALS AND METHODS

254 patients with stage III or IV (1992 AJCC staging system) histologically proven squamous cell carcinoma of the larynx were treated by a surgery and a postoperative radiotherapy between January 1993 and December 1996 at the Department of Otolaryngology, University School of Medical Sciences in Poznań and the Department of Radiotherapy at the Great Poland Cancer Center in Poznań. The standard evaluation prior to surgery included: a complete history, physical examination, chest radiographs, ultrasonography of the neck, complete blood counts and serum chemistry. Computed tomography (CT) of the larynx and pharynx was performed almost in 50% of patients. The patients' clinical and pathological staging was performed according to the recommendation of the American Joint Committee on Cancer (1992) [13]. Patients' characteristics are shown in *Table 1*.

Tab. 1. Patient's characteristics according to stage of disease.

Variables	Number of patients
male	236 (93%)
female	18 (7%)
pT3	179 (70%)
pT4	75 (30%)
pN0	132 (52%)
pN1	96 (38%)
pN2	26 (10%)

Abbreviations used in the table:

p – pathological classification

Surgery

Total laryngectomy with homolateral or bilateral lymph adenectomy of the neck has been performed. 196 patients undergone homolateral neck dissection and 58 patients bilateral neck dissection. Before surgery no patient had tracheostomy. Only patients with good performance status (Karnofsky scale as 70 and over) were included in the study. Patients with advanced stages of the disease in lymph nodes higher than pN2 and tumour stage lower than pT3 were excluded from the analysis due to different prognosis from other categories (pT3 – pT4 and pN0 – N2).

Radiotherapy

Charts of all patients were reviewed. Patients were treated with Co60 or 6 MV X-rays with the application of lateral portals encompassing the tumour bed and all neck lymph nodes. The conventional postoperative radiotherapy was given 5 times a week at dose of 2 Gy per fraction to the median total dose of 61.2 Gy (range: 57 – 64 Gy) to the tumour bed. The dose was calculated for the midline of the neck. A shrinking field technique with shielding of the spinal cord after dose of 44 Gy was introduced and then additional irradiation of the posterior lymph nodes with 9 MeV electrons to the dose of 50 Gy was continued. The lower neck lymph nodes were irradiated electively with an anterior field to a dose of 50 Gy.

The median time interval between surgery to the beginning of RT was 45 days. Patients after surgery waited for the beginning of RT due to the time needed for the pathological evaluation and the waiting time for RT at our center, which was about 3 - 4 weeks. The median time of the RT course was 47 days (range: 40-74 days). During radiotherapy some gaps were observed because of acute mucositis, concurrent diseases, breakdown of the therapeutic machine, problems with the transport of patients, and public holidays. The median time of the overall combined treatment time (OTT) was 92 days (range: 65 - 131 days). Patients' characteristic regarding the time factor are shown in *Table 2*.

Tab. 2. The time factor in the analysed group of patients.

Variables	**Days/Number of patients (pts)**
OTT	92 days (range 65 – 131)
interval between surgery and RT	45 days (range 22 – 78)
duration of RT	47 days (range 40 – 74)
interval time longer than 50 days	177 (69%) pts
RT duration longer than 44 days	73 (28%) pts
OTT longer than 90 days	141 (55%) pts
OTT longer than 100 days	76 (30%) pts

Abbreviations used in the table:

RT – radiotherapy
OTT – overall treatment time
pts – patients

The follow-up

After the completion of radiotherapy, all patients were evaluated for a local-regional control and complications, and survival by a multidisciplinary team of a radiation oncologist and a surgeon over 2-month intervals for the first 2 years, and at 6-month intervals for three and more years. Generally, 52 patients were lost from the follow-up for unknown reasons.

Statistical methods

The endpoint used in this study was the loco regional control (LRC) for the patients analyzed. Patients during the follow-up were considered to be failures when a recurrence either in the primary tumour bed or in the regional lymph nodes occurred, or in a case when distant metastases with regional failure were found concurrently. Patients who developed isolated distant metastases without any local-regional failure were censored at the time of the event. Patients who died of a concurrent disease without any evidence of a local-regional failure were censored at the time of the last follow-up.

The time factor was divided into following groups (categorical variables): the interval time between the surgery and the RT (less than 50 days and more than 50 days), the time of RT (below 44 days vs. over 44 days), the overall treatment time (up to 90 days vs. over 90 days and up to100 days vs. over 100 days). The time factor values (OTT, RT time, and the waiting time) were also analyzed as continuous variables.

The actuarial loco regional control (LRC) rate curves were estimated by the method of Kaplan and Meier [14]. Actuarial LRC rates were analyzed by univariate methods (the comparison of survival curves), which were performed using a log rank test [15]. A multivariate analysis was based on the Cox proportional hazard model including the following factors: age, sex, pathological nodal status, RTT, and interval time between surgery and radiotherapy.

RESULTS

The median follow-up was 4.5 years. The actuarial 5-year overall survival was 49%, the actuarial LRC rate for the entire group was 70% (*Fig. 1*). Following sites of the LRC relapses such as local (n = 8 patients), regional and regional with the presence of distant metastases (n = 78 patients) were observed.

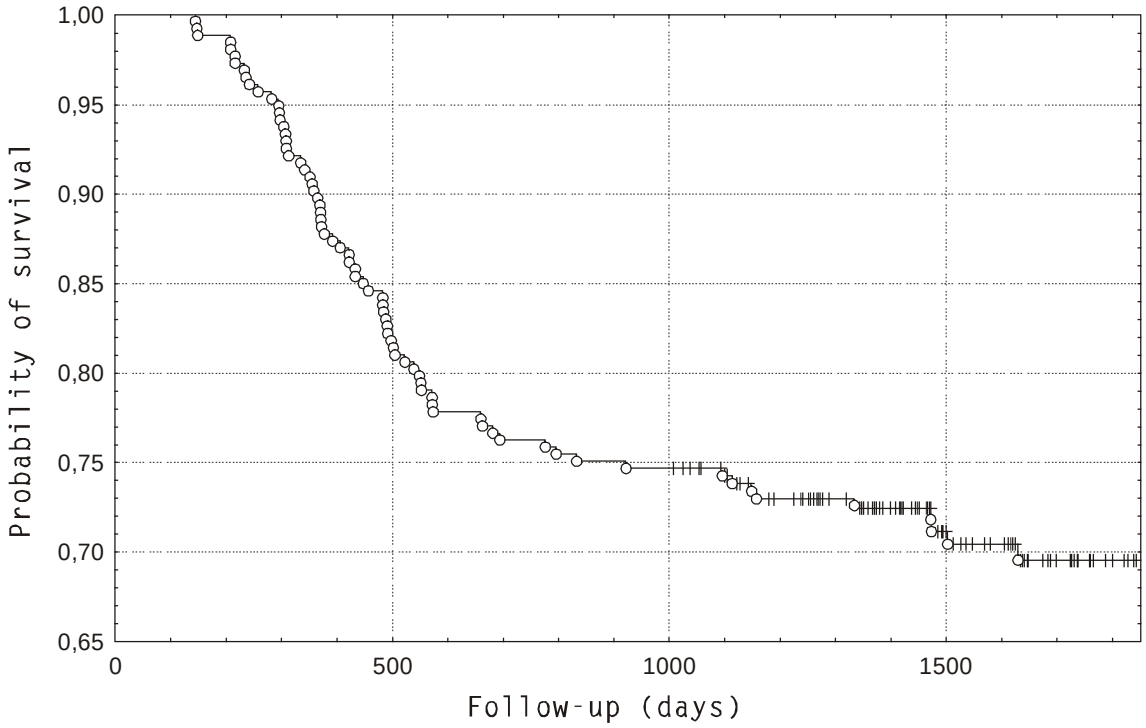

Fig. 1. The actuarial 5-year loco regional control for all 254 patients.

Tumour stage (pT3, pT4), patients' age, sex, the interval between surgery and the RT less than 50 days, and the RT time shorter than 44 days were not connected with a worse outcome of treatment.

The actuarial 5-year LRC rates in the group of patients treated by surgery and post-operative radiotherapy for pT3 and pT4 stage were 68%, and 72%, respectively (p = 0.2).

The univariate analysis (log-rang test) revealed that the involvement of lymph nodes (pN0 vs. pN1-2) was associated with worse results of combined treatment. In patients without any involvement of lymph nodes (pN0) the estimated 5-year LRC rate was 76%, but in the group of patients with metastases in lymph nodes (pN+) the LRC rate was 64%. The comparison of the two estimated curves for the status of lymph nodes was found to be statistically significant (p = 0.007, log-rang test).

Patients with the interval time between S and RT more than 50 days had the 5-year LRC rate 68% as compared with 72% for those with the time interval less than 50 days (p = 0.04). In the group of patients with involvement of lymph nodes (pN+) the negative influence of the prolongation of the waiting time (the time interval between surgery and the radiotherapy) on the outcome was more pronounced (p = 0.007) than in the group of patients (pN0) without metastases to the lymph nodes (p = 0.39).

The prolongation of the time of the RT beyond 44 days was connected with an increase in number of loco regional failures (p = 0.002, log-rang test).

The overall time of the combined treatment (OTT) longer than 90 days was correlated with the increased loco regional failure (p = 0.07, log-rang test). In the group of patients with the OTT longer than 100 days (n = 76) the 5-year LRC rate was 63% compared with 77% in patients with the OTT shorter than 100 days p = 0.0009) (*Fig. 2*).

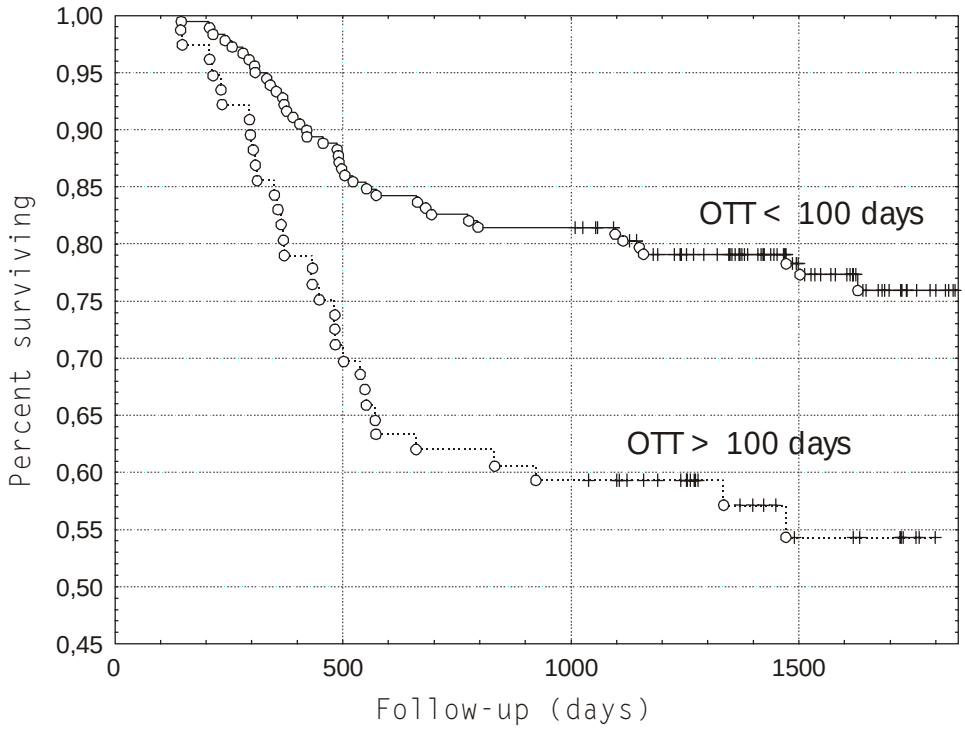

Fig. 2. The actuarial the 5-year locoregional control rate for the entire group of patients (n = 254) according to overall treatment of combined time.

The results of the multivariate analysis are shown in *Table 3*. The data in the table indicated that the pathological status of lymph nodes, the overall treatment time, and the time of radiotherapy were independent variables which had a great effect on the results of treatment. On the other hand, such variables as pT3/pT4, the interval time between surgery and radiotherapy, age, and sex were not independent prognostic factors for loco regional control in postoperative radiotherapy.

Tab. 3. The multivariate analysis for locoregional failure: the proportional Cox hazard model.

Variables	**hazard ratio**	**CI [95 %]**	**p**
T stage (pT3/pT4)	0.9	–	ns; 0.69
N stage (pN0/pN1-2)	1.34	1.29 – 1.39	0.035
Interval time (days)	1.01	–	ns; 0.04
Time of RT (44<days/ 44>days)	1.39	1.24 – 1.54	0.016
Age (years); <60/>60	0.85	–	ns; 0.51
Sex (male/female)	1.003	–	ns; 0.18

CI – confidence interval

ns – non significant

DISCUSSION

During the last few years the duration of radiotherapy has been demonstrated to be one of the most important prognostic factor in radiotherapy in head and neck cancers.

Our analysis was shown that the prolongation of the overall combined treatment time (from surgery to the end of radiotherapy) was associated with decreased loco regional control in advanced laryngeal cancer. Prolongation of both the overall treatment time and the time of radiotherapy (RTT) let to the decrease in locoregional control.

Numerous retrospective studies have indicated that the prolongation of RT alone in head and neck cancer had a negative effect on the outcome of treatment [10,11, 12,16,17,18]. The risk of failure connected with one additional day of irradiation time (protraction) in radiotherapy alone resulted in average loss of locoregional control by approximately 1 - 2%. The main factor responsible for such a negative adverse is the accelerated repopulation of clonogenic cells [19]. The definition of time in this work was based on the concept that the time factor should be considered as a total "package" in the context of accelerated repopulation [16,17,18].

Generally, the analysis of the time factor in postoperative radiotherapy is more complicated than in radiotherapy alone because of many unknown factors such as the amount of cancer cells prior to radiotherapy, post surgery changes in the blood flow in the operative field, and inflammatory cytokines which may influence the results of radiotherapy. After surgery the amount of cancer cells may differ in a broad spectrum and in some patients no cancer cells can be expected (no RT is needed), but on the other hand, the tumour bed or/and the entire network of lymph nodes of the neck (a microscopic disease) may contain 10^9 of cancer cells [20].

Inaccurate postoperative pathological evaluation of the margins of resections, particularly in patients with advanced disease (pT4) is another problem. According to Parsons et al. [8] and Looser et al. [21] in advanced head and neck cancer the evaluation of surgical margins in all possible directions is a great challenge for a pathologist, and such an evaluation in approximately of 40% of all cases is usually inaccurate. It is worth emphasizing that in this series recurrences in the primary tumour bed were observed only in 8 out of 254 patients (3%). The main field of recurrences were regional lymph nodes, and thus the more efficient treatment in this area may result in improvement in the outcome of treatment.

The third factor, which makes it difficult to evaluate the effect of the time factor on the outcome of postoperative treatment is the fact that accelerated repopulation is probably limited mainly to surgery fields (tumour bed and the area of lymph nodes dissection).

In our material, the high risk of subclinical involvement of lymph nodes was the main indication for the postoperative radiotherapy. Seventy-eight out of 254 patients had relapses in the neck and 50% of them relapsed within the first two years of the follow-up after the treatment completion. Another problem which occurred in our analysis was the loss of 52 patients from the follow-up which is common in the group of patients with an advanced stage of head and neck cancer.

We have excluded from the analysis a group of patients who represented a very advanced stage of the disease in lymph nodes established as N3 due to a very poor prognosis in this group. On the other hand, we also excluded patients with a low risk of local relapse (pT2). The main reason was enhancement of the homogeneity patients and treatment (surgery, dose of radiotherapy). The locoregional control rate (LRC) for an evaluation the effect of the time factors on the results of treatment in a combined treatment modality was chosen, because it estimates more properly local efficiency of radiotherapy than the overall survival. A simple comparison of the results of treatment based on the overall survival is problematic in head and neck cancer because of the high frequency of comorbidity illness and a high rate of the second malignancy due to a strong smoking abuse. In the population of patients with advanced stage of laryngeal cancer even after successful

treatment the risk of occurrence of a new site of origin of cancer disease in other organs like the lungs, esophagus is still high.

In the first phase of our analysis the log-rank test (univariate analysis) has shown that the prolongation of OTT, RTT, the interval time between surgery and radiotherapy, and involvement of lymph nodes were associated with a decrease in LRC rates.

The multivariate analysis (Cox proportional hazard model) indicated that the prolongation of the OTT and the time of RTT, and involvement of lymph nodes constituted independent prognostic factors for locoregional control. The time interval between surgery and radiotherapy was important, but multivariate analysis did not confirm this is an independent prognostic factor for combined treatment. A more negative influence on the results of treatment was due to the protraction of the radiotherapy (RTT) rather than to the time interval between surgery and radiotherapy. Similar observations made Parson et al. [8] were based on a study of postoperatively irradiated patients with cancer of the oral cavity. According to this report the attention should be focused on the time interval between surgery and irradiation and the time of radiotherapy.

Finally, we can conclude that patients with more aggressive biology of the disease (pN2, infiltration of lymph node capsule) and advanced stage needed a more intensive treatment such as accelerated radiotherapy or concurrent radio-chemotherapy [22,23,24].

CONCLUSIONS

The prolongation of the overall treatment time of a combined modality leads to a decrease in the locoregional control in a group of patients with advanced laryngeal cancer. This negative effect was a result was an effect of the prolongation of both the time of adjuvant RT and the time interval between surgery and RT, the impact of the latter factor being smaller.

REFERENCES

1. Razack MS, Maipang T, Sako, Bakamjian V, Shedd D. Management of advanced glottic carcinomas. Am J Surg 1989;158:318-20.
2. Huang DT, Johnson CR, Schmidt-Ullrich R, Grimes M. Postoperative radiotherapy in head and neck carcinoma with extracapsular lymph node extension and/or positive resection margins: a comparative study. Int J Radiat Oncol Biol Phys 1992; 23(4):737-42.
3. Vikram B, Strong EW, Shaw J, Spiro RH. Elective postoperative radiation therapy in stage III and IV epidermoid carcinoma of the head and neck. Am J Surg 1980; 140:580-4.
4. Lundahl RE, Foote RL, Bonner JA, Suman VJ, Lewis JE, Kaperbauer JL, McCaffrey TV, Olsen KD. Combined neck dissection and postoperative radiation therapy in the management of high-risk neck: a matched-pair analysis. Int Radiat Oncol Biol Phys 1998;40(3):529-34.
5. Vikram B, Strong EW, Shaw JP, Spiro R. Failure in the neck following multimodality treatment for advanced head and neck cancer Head Neck Sur 1984;6(3):724-9.
6. Department of Veterans Affairs Laryngeal Cancer Study Group, Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 1991; 324:1685-90.
7. Kramer S, Gelber RD, Snow JB, Marcial VA, Lowry LD, Davis LW, Chandler R. Combined radiation therapy and surgery in the management of advanced head and neck cancer: final report of study 73-03 of the Radiation Therapy Oncology Group. Head Neck Surg 1987;10(1):19-30.
8. Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR. An analysis of factors influencing the outcome of postoperative irradiation for squamous cell carcinoma of the oral cavity. Int J Radiat Oncol Biol Phys 1997;39:137-48.
9. Maciejewski B, Preuss-Bayer G, Trott KR. The influence of the number of fractions and overall treatment time on local control and late complication rate in squamous cell carcinoma of the larynx. Int J Radiat Oncol Biol Phys 1983;9:321-8.
10. Skladowski K, Tarnawski R, Maciejewski B, Wygoda A, Ślosarek K. Clinical radiobiology of glottic T1 squamous cell carcinoma. Int J Radiat Oncol Biol Phys 1999;43: 101-6.

11. Fowler JF, Lindstrom MJ. Loss of local control with prolongation in radiotherapy. Int J Radiat Oncol Biol Phys 1992;23(2): 457-67.

12. Trott KR. Cell repopulation and overall treatment time. Int J Radiat Oncol Biol Phys 1990;19:1071-5.

13. American Joint Committee on Cancer, (1992) Manual for staging of cancer. Philadelphia, PA: Lippincott JB.

14. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations J Am Stat Assoc 1958;53:457-81.

15. Cox DR, Oakes D. Analysis of survival data. London: Chapman and Hall; 1974.

16. Garden AS, Weber RS, Ang KK, Morrison WH, Matre J, Peters LJ. Postoperative radiation therapy for malignant tumors of minor salivary glands. Cancer 1994;73:2563-9.

17. Byers RM, Clayman GL, Gulliamondegui OM, et al. Resection of advanced cervical metastases prior to definitive radiotherapy for primary squamous carcinoma of the upper aero digestive tract. Head Neck 1992; 14:133-8.

18. Vikram B, Strong EW, Shah JP, Spiro R. Failure in the neck following multimodality treatment for advanced head and neck cancer. Head Neck Surg 1984;6:724-9.

19. Withers HR, Peters LJ. Transmutability of dose and time. Commentary on the first report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000;48:1-2.

20. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol. 1988;27:131-46.

21. Looser KG, Shah JP, Strong EW. The significance of positive margins in surgically resected epidermoid carcinoma. Head Neck Surg 1978;1:107.

22. Trotti A, Klotch D, Endicott J, Ridley M, Cantor A. Postoperative accelerated radiotherapy in high-risk squamous cell carcinoma of the head and neck: Long-term results of prospective trial. Head Neck 1988;20:119-23.

23. Brizel DM, Albers MA, Fisher SR, Scher RL, Richtsmeier WJ, Hars V, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med 1998;328:1798-804.

24. Forastiere AA, Trotti A. Radiotherapy and concurrent chemotherapy: a strategy that improves locoregional control and survival in oropharyngeal cancer. J Natl Cancer Inst 1999;91:2065-6.