

# ADJUVANT RADIOTHERAPY IN LARYNGEAL CANCER OVER THE LAST FEW DECADES: THE EVOLUTION OF TREATMENT POLICY IN THE GREAT POLAND CANCER CENTRE

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## SUMMARY

**Aim:** to evaluate changes in the treatment trends of the larynx cancer over the last few decades concerning the time factor in postoperative radiotherapy (OTT) after total laryngectomy and defining the target in adjuvant radiotherapy after partial laryngectomy with the reconstruction of the larynx.

**Material and methods:** The first part of the analysis was based on the comparison of OTT in two groups of patients (group A and B) irradiated postoperatively after total laryngectomy. Group A consisted of 311 patients who were treated between 1986 and 1990. The postoperative radiotherapy (RT) was given 5 times a week at the daily dose of 2 Gy per fraction to the mean total dose of 61.2 Gy (range: 57-66 Gy), the mean time of the RT course was 47 days (range: 40-74 days). Group B encompassed 270 patients treated with a similar technique in the years 2000-2002 with the same fraction and total dose.

The second part of the analysis concerning the change of strategy in relation to the indication for adjuvant radiotherapy after partial laryngectomy (supracricoid laryngectomy with cricothyroidopexy, cricothyroidoepiglottopexy, horizontal laryngectomy, and fronto-lateral laryngectomy) during the last decade. The analysis was based on the review of patients who were treated between 1996 and 2002 at our department. One of the main aims of radiotherapy technique was to avoid the irradiation of a newly reconstructed larynx. All patients were irradiated postoperatively in a conventional way to the elective dose of 50 Gy to the neck with a boost dose from 10 to 16 Gy to the bed of the removed lymph nodes. Acute and late morbidities were evaluated according to the RTOG/EORTC morbidity scoring system.

**Results and conclusion:** In group A gaps were observed in 52% of all the treated patients and their mean time was 8.2 days (range: 1-16 days). In group B gaps occurred in 26% of all treated patients with the mean gaps duration of 4.2 days (range: 1-15 days). The first part of the analysis revealed a significant time reduction in gap duration (4.2 days) and their frequency (26%) in the last decade ( $p=0.002$ ).

The second part of the analysis showed that the protection of the newly reconstructed larynx led to the avoidance of significant side effects. Combined treatment, which consisted of partial laryngectomy and adjuvant RT of the neck with the protection of larynx, plays an important role in the decrease of treatment morbidity and makes it possible to preserve laryngeal function.

**Key words:** time factor, gaps, total laryngectomy, partial laryngectomy, adjuvant radiotherapy, toxicity.

## INTRODUCTION

Radiotherapy is one of the most important methods of treatment in laryngeal cancer but in more advanced stages of the disease it is mainly advocated as a post-operative method of treatment. The duration of the radiotherapy course is considered as one of the clinical factors which can significantly result in locoregional con-

trol (LRC) [1-4], which has been confirmed by considerable evidence based on retrospective analyses. Generally, it has been established that prolongation by one day of RT course is connected with a drop in LRC in the range from 1% to 2% [2-4]. These facts have changed the policy of treatment in radiotherapy departments related to the time factor.

Routine application of adjuvant RT, which encompassed the reconstructed larynx for patients after partial laryngectomy with the reconstruction of the larynx, produces a large number of side effects [5-8]. Thus, postoperative radiotherapy is reserved to individual patients, only when such a treatment may produce benefit. In the case of metastases in the neck such combined treatment lead to therapeutic gain.

In this work, we have evaluate the policy of treatment over the last decade at our department related to the time factor (gaps) in adjuvant RT after total laryngectomy and target definition in adjuvant RT after partial laryngectomy.

## **MATERIAL AND METHODS**

### ***The time factor (gaps during adjuvant radiotherapy)***

Two groups of patients were distinguished on the basis of the following periods of treatment: group A (311 patients) treated between January 1986 and December 1990, and group B (270 patients) treated in the years 2000-2002. The charts of all patients selected in this analysis were reviewed retrospectively. All patients were in stage III or IV (1992 AJCC staging system) of the histologically proven squamous cell carcinoma of the larynx. In each case, a surgery at the Department of Otolaryngology, Poznań University of Medical Sciences and a postoperative RT at the Department of Radiotherapy at the Great Poland Cancer Center in Poznań were performed. The conventional postoperative RT was given 5 times a week at the daily dose of 2 Gy to the mean total dose of 61.2 Gy (range: 57-66 Gy) to the tumour bed in the first group, and the mean dose of 62,2 Gy (range: 58-68 Gy) in the second group. In each case, additional lower neck field was applied to the total dose of 50 Gy. During RT some gaps in both groups of patients were observed.

### ***Target in postoperative radiotherapy after partial laryngectomy***

This part of the analysis was based on the retrospective review of patients treated at our departments. The combined treat-

ment for the patients analyzed consisted of partial laryngectomy with selective neck dissection and adjuvant RT. The following conservative techniques of partial laryngectomy in both groups were carried out: supraccricoid laryngectomy with cricothyroidopexy (CHP), cricothyroidoepiglottopexy (CHEP), horizontal laryngectomy, and frontolateral laryngectomy. Homolateral or bilateral selective lymph nodes dissection was performed in all patients suspected of metastases to the lymph nodes during ultrasonography examination. Only patients with good performance status (Karnofsky scale as 70 or above) and under the age of 60 were included in this study. The postoperative RT was only recommended in the case of pathologically confirmed metastases to the neck with additional risk factors such as extracapsular infiltration, or multiple metastases or positive postoperative margin. It is necessary to add that the neck was the only target for RT with additional protection of the newly reconstructed larynx. Patients were treated with 6 MV X-rays with the application of two lateral portals encompassing selectively all neck lymph nodes. The conventional postoperative RT was given 5 times a week at the dose of 2 Gy per fraction to the median total dose of 50 Gy to all the lymph nodes with individual shielding of the reconstructed larynx. During the second phase of RT an additional dose (boost) of 16 Gy was added to the region of high risk of recurrence e.g. to the bed of the removed metastatic lymph node. It should be emphasized that treatment planning was based on CT planning in all patients, the majority of whom were also given three-dimensional conformal radiotherapy planning and treatment procedure (3D CRT). This procedure provided better shielding of the reconstructed larynx.

The analyzed group of patients encompassed 17 patients who were treated between January 1996 and March 2002: 10 patients underwent homolateral neck dissection, and 7 patients bilateral neck dissection. The pathological report revealed pN1 metastases in 11 cases and pN2 in 6 cases (metastases were found in the regions II and/or III). Patients treated experienced only some worsening in the quality

of voice. The mean time of the follow-up was 5 years (range: 1 to 6 years).

The follow-up

After the completion of adjuvant radiotherapy, all patients were evaluated for side effects (acute and late) according to the Radiation Therapy Oncology Group (EORTC/ RTOG) scoring system. During radiotherapy no gaps were noted because of side effects related to RT.

## RESULTS

### *Gaps in adjuvant radiotherapy*

During RT some gaps in both groups were observed because of acute mucositis, concurrent diseases, breakdown of the therapeutic machine, problems with the transport of patients, and public holidays. The mean duration of gaps in group A was 8.2 days (range: 1-16 days). In this group, gaps were observed in 52% of all patients treated. In the second group (group B) the mean duration of gaps was 4.2 days (range: 1-15 days), and the rate of gaps in radiotherapy was 26% of all patients irradiated. The statistical analysis (test Mc Nemary) revealed that this observation is statistically significant ( $p= 0.002$ ).

### *Target in partial laryngectomy*

The crude 3-year overall survival rate was 17/17, and the LRC rate for the entire group was 1/17. All patients completed the entire course of radiotherapy without any gaps. No significant acute and late side effects (oedema, dyspnoea, dysphagia or pain) were observed. Toxicity concerning the skin and mucosa of the pharynx grade 1 or 2 according to the RTOG/EORTC classification was observed. No acute and late side effects grade 2 and 3 were observed.

## DISCUSSION

In advanced laryngeal cancer, combined treatment consisting of surgery and postoperative radiotherapy is a standard treatment in many centres across the world [9,10]. 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

tumors and pN1 or pN2 or pN3 neck disease [9, 10].

In 1988, Withers and co-workers [11] indicated that the prolongation of the radiotherapy treatment time in head and neck cancer had very negative effect on locoregional control of the disease. Numerous retrospective data from literature showed that the protraction of RT alone or postoperative RT caused a substantial drop in the LC of disease [1-3]. The accelerated repopulation of clonogenic tumour cells is responsible for such negative effect of the time factor [4]. This fact has been known since the 1990s, but it is also known that the introduction of a new standard of treatment in routine clinical practice based on the results of clinical trials takes some time, which may widely differ from institution to institution. The reasons for the later introduction of the new standard of treatment are: organizational problems, previous experience, anxiety about the side effects, old habits etc. During the last decade at our department the mean time of gaps reduction during treatment time was 4.2 days, but there still exists a place for improvement. In the years 1986-1990 the occurrence of gaps during the course of postoperative RT was 52%, but in the years 2000/02 it dropped to 26%. Unexpectedly, in the last few years, some gaps were caused mainly by holidays and acute morbidity. The latest changes in the organization of our department related have provided some possibility of additional irradiation on Saturdays when some breaks occurred during irradiation caused by holidays or breakdown of therapeutic machines. This made it possible to reduce the treatment time and eliminate the effect of unexpected gaps in the course of RT. In addition, it has been reduced the gaps caused by acute side effects by introducing more intensive supportive treatment of patients during irradiation.

Another issue, which addressed in this paper, involves the definition of a target for adjuvant RT in partial laryngectomy with the reconstruction of the larynx. Developments in microsurgery of laryngeal cancer allow introducing this method of treatment in routine clinical practice. These surgical techniques are alternatives

to total laryngectomy and/or curative radiotherapy [12,13]. The most popular techniques of conservative surgery are supra-cricoid laryngectomy with the reconstruction of the larynx (cricohyoidopexy and cricohyoidoepiglottopexy), supraglottic laryngectomy, and horizontal laryngectomy [14]. These techniques make it possible to preserve voice function with the natural passage of air during the breathing process and at the same time give the possibility for an adequate removing of the tumour.

Our analysis has shown that adjuvant radiotherapy of the neck after conservative surgery of the larynx with selective neck dissection with metastases to the neck was associated with excellent LC without any clinically significant acute and late morbidity of the operated on larynx. These results were possible since the irradiation was focused on the neck with the protection of the larynx. After surgery in the case of metastases to the neck the amount of cancer cells may differ over a broad spectrum and in some patients no cancer cells can be expected (no RT is needed). On the other hand, the network of lymph nodes of the neck (a microscopic disease) may contain  $10^9$  of cancer cells. For this reason, one of the most important indication for adjuvant radiotherapy of the neck in patients with head and neck cancer are metastases, especially those with extracapsular infiltration.

Another factor, which should be taken into account, is the fact that accelerated repopulation of clonogenic cells is probably limited mainly to surgery fields (the area of lymph nodes dissection) and for this reason the implementation of radiotherapy with additional dose (boost) to the scar may positively effect the results of combined treatment. In our material, the high risk of subclinical involvement of lymph nodes in the neck was the indication for the adjuvant radiotherapy. We could not perform any statistical analysis with patients who were irradiated on the entire new reconstructed larynx because before 1996 the postoperative irradiation in case of partial laryngectomy was not performed.

The primary aim of the treatment in larynx cancer is cure, but also another as-

pect of the treatment should be considered in each case. This is the patient's quality of life after the completion of the treatment. In general, it can be said that treatment is a specific kind of "game" or "battle" between the killings of cancer cells and protecting the healthy ones. What is especially important for patients with the larynx cancer is to have the function of this organ preserved. Thus, function preserving treatment should be considered in each and every patient. Generally, we can choose between surgery and primary radiotherapy. Thus, only one method of treatment should be carried out and the combination of both procedures is unreasonable due to increased economical costs and higher morbidity. Generally, numerous data from the literature indicate that the chances of local control in radiotherapy alone decrease significantly with the increase in the tumour volume, which is to be expected for larger of T2 or T3 tumours [10]. Thus, at our department surgery is the preferred policy of treatment, but in the cases when, after partial laryngectomy, the pathological examination after selective neck dissection revealed metastases to the neck the question arose as to the application of adjuvant radiotherapy. The simplest answer is to advocate the application of postoperative radiotherapy. On the other hand, numerous retrospective data indicate that the irradiation of a newly reconstructed larynx is controversial due to the high risk of late toxicity concerned the larynx. Laccourreye et al. [8] from their retrospective study of 90 patients established that severe complications after combined treatment occurred in 15 patients. Severe complications, which led to the death of 3 patients (3.3%), permanent gastrostomy in 3 (3.3%), and permanent tracheostomy one patient (1.1%). These authors have reported that the mean dose delivered to the larynx was the only variable statistically related to the incidence of severe complications.

In another study, conducted by Spriano et al. [15], postoperative radiotherapy was added for presumed microscopic disease at the primary site (the larynx), regional nodes, or both. The 2- and 5-year actuarial locoregional control values were 85% and 83%, respectively. Thirty patients (54%)

developed laryngeal complications. However, only one patient experienced grade 4 laryngeal oedema requiring permanent tracheostomy. At multivariate analysis, the treated volume ( $p=0.03$ ) and, the total dose to the larynx ( $p=0.03$ ) were significantly associated with a high level of local toxicity. In the conclusion the authors stated that after partial laryngectomy, postoperative radiotherapy to the neck did not affect local morbidity when careful radiotherapy planning was implemented to avoid the irradiation of the larynx.

A similar treatment strategy to ours was presented by Wang et al. [16] as these authors applied radiotherapy only to the neck. This made it possible to preserve the vocal and swallowing function without serious complications. It is worthy underlining that radiotherapy was added in the case of positive margins, vascular invasion, and extranodal spread of disease. Similar indications for adjuvant radiotherapy were applied in our group of patients. Finally, the authors stated that they did not observe any major problems involving postoperative wound healing or airway management during radiation treatment. Gregor et al [6] on the basis of their on his analysis of 89 patients who underwent partial laryngectomy combined with postoperative radiotherapy of the neck postulated that no additional toxicity from the larynx could be expected when radiotherapy was applied only to the neck. Also Lutz et co-workers [8] showed that postoperative radiotherapy improved the results of treatment. According to these investigators, in the group of patients without irradiation of the neck the 23% regional recurrences were observed. On the other hand, the introduction of adjuvant radiotherapy allowed to decrease the risk of local failure to 8%.

It is obvious that postoperative radiotherapy in patients without any significant risk factors for regional recurrence should be also ruled out and such a strategy of treatment was introduced in our departments.

Generally, for all head and neck cancers in the case of pathologically proved metastases (pN1 with extracapsular infiltration, pN2) to the lymph nodes adjuvant radiotherapy is advocated [17]. On the other hand, the application of postoperative

radiotherapy in patients after partial laryngectomies with the reconstruction of the larynx led to the increase in acute and late side effects in the larynx. Therefore, such a combined strategy may cause some controversies due to the negative effect of irradiation on the physiological function of the newly reconstructed larynx [6,18]. Oedema of mucosa and cartilage may even lead to the necrosis and the need for permanent tracheostomy [8]. Changes that led to the protection of the new reconstructed larynx allowed us to avoid some serious complications of treatment. The efficacy of radiotherapy did not change but the toxicity was reduced. It is worth adding that such combined treatment is only indicated in individual cases [19].

## CONCLUSIONS

In the last decade, at our department the gap in postoperative radiotherapy in laryngeal cancer dropped from 8.2 to 4.2 days and the percentage of gaps dropped from 52% to 26%.

By focusing irradiation only to the neck, with the protection of the newly reconstructed larynx, which is assumed to be an organ at risk apart from the spinal cord, made it possible to introduce this type of irradiation with minimum side effects in patients after partial laryngectomy with reconstruction in the case of pN1 with extracapsular infiltration and pN2 metastases.

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