HYPERFRACTIONATION AS AN ALTERED FRACTIONATION REGIMEN IN PRIMARY RADIOTHERAPY FOR SQUAMOUS CELL CARCINOMA OF THE LARYNX

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Abstract: The aim of the study was to investigate the efficacy of hyperfractionation as an altered fractionation treatment schedule in comparison with conventional fractionation in primary definitive radiotherapy for laryngeal squamous cell carcinoma. From March 1999 to December 2000, a group of 28 patients with previously untreated squamous cell carcinoma of the larynx were irradiated with conventional fractionation to total doses of 66 to 70 Gy in 33 to 35 fractions/6.5 to 7 weeks, 2 Gy/fraction/day, 5 days/week. From January 2001 to June 2004, the other 27 patients with the same diagnosis, were treated prospectively with hyperfractionation receiving radiotherapy delivered at 1.2 Gy/fraction, twice daily, 5 days/week to 74.4 to 79.2 Gy/62 to 66 fractions/6.2 to 7 weeks.

Complete response rates after two months of radiotherapy completion were 78.6% (22 of 28) and 66.7% (18 of 27) in the conventional fractionation and hyperfractionation group, respectively (Fisher exact test; P = 0.246). The two year loco-regional control rates were 61.0% ± 18.1 (95% CI) in the conventional fractionation group and 45.0% ± 18.8 (95% CI) in the hyperfractionation group (log-rank test; P = 0.075). Overall survival rate at two years was 71.0% ± 16.8 (95% CI) for the conventional fractionation group and 43.0% ± 18.7 (95% CI) for the hyperfractionation group (log-rank test; P = 0.071).

The absence of statistically significant differences either in loco-regional control or overall survival observed between the two treatment modalities suggested that hyperfractionation regimen was not more efficacious than conventionally fractionated radiotherapy for previously untreated carcinoma of the larynx.
**Key words:** head and neck cancer, laryngeal cancer, radiotherapy, conventional fractionation, hyperfractionation.

**Introduction**

In early-stage squamous cell carcinomas of the larynx, both surgery and radiotherapy are equally effective. However, the treatment of tumors of the larynx requires consideration of two vital issues that heavily impact on the patient’s quality of life, namely, speech and swallowing [1]. The therapeutic strategy should consider preservation of the vocal function and swallowing without aspiration [2]. In most advanced-stage laryngeal cancers combined treatment with surgery followed by radiotherapy is recommended [3]. However, the possible advantage in survival after surgery and postoperative radiotherapy compared to primary radiotherapy might be decreased by the increased risk of second primary tumors and also of death from inter-current disease in patients cured of their laryngeal carcinoma, which is also another important criterion when considering the choice of preferred treatment. During the last two decades radiochemotherapy by means of induction and/or concomitant chemotherapy as a complex treatment strategy using different radiochemotherapy regimens as a part of organ preservation program enabled preservation of the larynx in nearly 70 percent of patients with advanced laryngeal carcinoma, otherwise requiring total laryngectomy [4, 5]. On the other hand, there always must be a theoretical concern that chemotherapy may be immunosuppressive, allow for the emergence of radioresistant tumor cell clones, or lead to accelerated repopulation of tumor cells that are less sensitive to radiotherapy that is in accordance with reviews and meta-analyses that showed little or no benefit of induction chemotherapy, as compared to radiotherapy alone [6, 7]. Lefebvre and Bonneterre [8] revealing the current status of larynx preservation trials emphasize that the results of definitive radiotherapy are comparable with the results of total laryngectomy with postoperative radiotherapy in larynx cancer patients. Given that radiotherapy as a single treatment modality is an opportunity for achievement of satisfactory loco-regional control rates, as well as for enabling functional organ preservation, it is not surprising that clinical investigations of rational modification of radiation fractionation regimens have been done in order to provide more effective tumor control using higher doses of irradiation given more intensively [9]. Such efforts for improving the tumor control probability correspond the fact that loco-regional disease progression remains the dominant type of treatment failure in laryngeal cancer [10].

Hyperfractionation is one of the two prototypes of altered radiation fractionation regimens. Hyperfractionated radiotherapy uses smaller than conventional fraction sizes (e.g., 1.0 to 1.2 Gy) administered two or more times per day to total doses higher than conventional; overall treatment times are roughly the same as for conventionally radiotherapy. The rationale for hyperfractionation as
A separate concept of altering the fractionation schedule is its potential to increase the total dose — translating into a higher probability of loco-regional control without an increase in late toxicity because of the reduction of fraction size [11, 12]. Hyperfractionation is mainly based on the principle of high fractionation sensitivity of late-responding tissues that allows delivering of high total doses by using low doses per fraction within the tolerance of normal tissues responsible for late effects. Modifying the dose per fraction has more effect on late-responding tissues, and, with lower doses, there is greater repair of these tissues than the ones involved in acute reactions. Hyperfractionation attempts to take advantage of these differing normal tissues responses which are a consequence of the differences in repair between acute- and late-responding tissues. This differential sensitivity is believed to be due to differences in the shapes of the dose-survival curves between late-effects and acute-effects (or tumor) tissues [11, 12, 13, 14]. The approach of hyperfractionation may also be effective by using the phenomenon of redistribution. Redistribution through the cell cycle that rapidly restores proliferating tumor cells in their initial and relatively more radiosensitive asynchronous state, use to be more effective whenever the number of inter-fraction intervals is increased such as the case with hyperfractionation where multiple daily fractions with lower doses per fraction are accomplished [15, 16].

The aim of our study was to analyze the results obtained by the use of hyperfractionation as an altered radiation fractionation in comparison with the results achieved by using conventional fractionation in definitive radiotherapy of laryngeal squamous cell carcinoma.

Material and Methods

From March 1999 to June 2004, 55 previously untreated patients, 50 men and 5 women, median age 58.3 years (range 39–73), with histologically proved squamous cell carcinoma of the larynx were entered in a retrospective-prospective study conducted in the Institute of Radiotherapy and Oncology in Skopje. The retrospective part of the study was represented by a retrospective control group consisted of 28 (50.9%) patients treated with conventionally fractionated radiotherapy during the period immediately preceding the start of twice-a-day protocol (from March 1999 until December 2000). From January 2001 to June 2004, the other 27 (49.1%) patients were treated prospectively with hyperfractionated radiotherapy. Exceptions occurred when patients either refused treatment with two daily fractions or were not offered twice-a-day irradiation because of lack of machine time.
The inclusion criteria were: age 18–75 years, Karnofsky performance status (Karnofsky index) \( \geq 60\% \) and all stages except stage IVC (TNM classification according to UICC and AJCC from 1997) \[17\]. Pretreatment diagnostic work-up other than medical history and physical examination consisted of panendoscopy with tumor biopsies to obtain the histological proof, neck ultrasound and fine-needle biopsy to obtain cytological proof of cervical metastases, blood chemistries, chest x-ray and liver ultrasound. The extent of the disease was also defined by computed tomography scanning and/or magnetic resonance imaging.

The conventionally fractionated radiotherapy schedule was 66 to 70 Gy in 6.5 to 7 weeks (one fraction of 2 Gy per day, 5 fractions per week). The hyperfractionation treatment schedule was 74.4 to 79.2 Gy in 6.2 to 7 weeks (two fractions of 1.2 Gy per day, 10 fractions per week with inter-fraction interval of at least 6 hr).

Radiotherapy was delivered using cobalt-60 machine with a source-to-surface or source-to-isocenter distance of 80 cm. During the first part of treatment, two large opposed lateral fields were usually used to treat the primary tumor and the lymph nodes in the upper neck. There was no elective nodal irradiation in patients with early glottic cancer. For patients with stage III/IV disease an anterior field was added to treat the supraclavicular nodes. For these patients with stage III/IV disease a shrinking-field technique was adopted. The first field reduction off the spinal cord occurred at 46 Gy for conventional fractionation and 45.6 Gy for hyperfractionation. The second field reduction occurred at 56 Gy for conventional fractionation and 55–57.6 Gy for hyperfractionation. Electrons or partial semi field technique were used for boosting the dose to involved nodes in spinal chains while protecting the cord. In patients irradiated with hyperfractionation these fields and the low neck field were treated once a day. The tumor dose was defined as the mid-line dose on the central axis for the parallel opposed fields and at 30 mm depth in the supraclavicular fossae for the direct anterior field.

According to our follow-up policy, the patients were seen for clinical examination monthly during the first year after they completed treatment, every 2 months for the second year, every 4 months for the third year, every 6 months in years 3–5, and annually thereafter. Tumor response was documented by direct measurement at every examination. Clinically suspected persistence or regrowth was biopsied when feasible. Complete response was defined as the absence of any clinical evidence of cancer two months after completion of radiotherapy. For estimating the loco-regional control rates, the following definitions for failures were used: patients who initially achieved only partial response to the
planned radiotherapy were considered failures on study day 1; patients who did achieve an initial complete response were considered as failures on the study day when a recurrence either in the primary or the node was first reported. Loco-regional control was defined as persisting tumor clearance above clavicles after complete response at the end of radiotherapy.

**Statistical analysis**

Association between categorical data was analyzed using contingency tables and tested according to the $\chi^2$ test. Fisher’s exact test was used when contingency tables had frequencies less than 5 [18]. Actuarial loco-regional control and survival curves were plotted according to Kaplan-Meier method [19] and compared by the log-rank test [20].

**Results**

The percentage of male patients was 89.3% (25 out of 28) in conventional fractionation group and 92.6% (25 out of 27) in hyperfractionation group. The median age was 57.4 years (range 39–73) in the group of patients treated with conventional fractionation and 59.2 years (range 39–73) in the group irradiated with hyperfractionation. Most of the patients had Karnofsky index of 80–100%, i.e. 92.9% (26 out of 28) in the conventional fractionation group and 96.3% (26 out of 27) in the hyperfractionation group. The distribution of sex (Fisher exact test; $P = 0.518$), age ($\chi^2$ test; $P = 0.904$), and Karnofsky performance status (Fisher exact test; $P = 0.514$), were not significantly different in the two treatment groups. The distribution of the patients according to the clinical stage of the disease is given in Table 1. The distribution of tumor related variables such as T stage, N stage and UICC/AJCC stage of disease were also not significantly different in the two treatment groups ($\chi^2$ test; $P = 0.938$, $P = 0.518$, $P = 0.680$, respectively).

All patients in each treatment group completed the assigned treatment in accordance with the protocol or with minor variations. The average total dose delivered at mid-depth of the central axis of the parallel-opposed fields was 69.1 Gy ± 4.14 standard deviation (SD) for patients irradiated with conventional fractionation and 78.5 Gy ± 1.30 SD for patients receiving hyperfractionation. The average overall treatment time was 51.2 days ± 4.14 SD for patients treated with conventionally fractionated radiotherapy, while hyperfractionation was accomplished in an average time of 47.7 days ± 3.59 SD.
Complete response to treatment was observed in 22 out of 28 patients (78.6%) in the group irradiated with conventional fractionation and in 18 out of 27 patients (66.7%) in the group treated with hyperfractionation (Fisher exact test; P = 0.246).

Loco-regional control and overall survival rates were analyzed in function of the different treatment schedules. Results of Kaplan-Meier estimates of loco-regional control and overall survival are shown in Figs. 1–2. Actuarial local control rates at two years were 61.0% ± 18.1 (95% CI) and 45.0% ± 18.8 (95% CI) for the conventional fractionation group and hyperfractionation group, respectively (log-rank test; P = 0.075; Fig. 1). The actuarial 2-year overall

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**Table 1 – Таблица 1**

*Tumor characteristics according to fractionation regimen*  
*Карактеристики на тумор по режим на фракциониране*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Conventional fractionation (N = 28)</th>
<th>Hyper-fractionation (N = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>2 (7.1%)</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>T2</td>
<td>7 (25.0%)</td>
<td>8 (29.6%)</td>
</tr>
<tr>
<td>T3</td>
<td>17 (60.8%)</td>
<td>16 (59.3%)</td>
</tr>
<tr>
<td>T4</td>
<td>2 (7.1%)</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td><strong>N stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>17 (60.8%)</td>
<td>14 (51.9%)</td>
</tr>
<tr>
<td>N1</td>
<td>6 (21.4%)</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>N2</td>
<td>5 (17.9%)</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>N3</td>
<td>0 (0%)</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td><strong>UICC/AJCC Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2 (7.1%)</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>II</td>
<td>6 (21.4%)</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>III</td>
<td>14 (50.0%)</td>
<td>11 (40.7%)</td>
</tr>
<tr>
<td>IVA</td>
<td>6 (21.4%)</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>IVB</td>
<td>0 (0%)</td>
<td>2 (7.4%)</td>
</tr>
</tbody>
</table>

* Because of rounding, not all percentages total 100.  
* Поради заокругляване, збирот на сите проценти не изнесува секогаш 100.
survival was 71.0% ± 16.8 (95% CI) for the conventional fractionation group and 43.0% ± 18.7 (95% CI) for hyperfractionation group (log-rank test; $P = 0.071$; Figure 2).

\[
\chi^2 = 3.198 \\
D. F. = 1 \\
P = 0.075
\]

Graphic 1 – Loco-regional control according to fractionation regimen
Графикон 1 – Локорегионална контрола според режимите на фракциониране

The most common sites of failure were in the primary site and/or in the neck nodes in both treatment groups. Loco-regional recurrence following complete response after radiotherapy was demonstrated in 6 out of 22 (27.3%) patients in the conventional fractionation group and in 4 out of 18 (22.2%) patients in the group treated with hyperfractionation. At the time of this analysis 12 out of 28 (42.9%) patients in the conventional fractionation group and 13 out of 27 (48.1%) patients in the hyperfractionation group have had loco-regional failures. Three (10.7%) patients in the group treated with conventionally fractionated regimen and 3 (11.1%) patients in the group treated with hyperfractionated regimen developed distant metastases with or without loco-regional failure.

**Discussion**

Hyperfractionation as an altered fractionation regimen accomplished in the prospective part of our study was based upon the theoretical basis for hyperfractionated radiotherapy described by Withers [21] and Thames et al. [11]. This strategy that exploits the difference in the fractionation sensitivity between rapidly and slowly turning over tissues was expected to improve the tumor control probability in patients with laryngeal carcinoma by increasing the total...
tumor dose without increasing the overall treatment time. However, despite our expectations at the beginning of the study that we would be able to confirm the superior efficacy of hyperfractionation regimen, the results thereof showed that no statistically significant differences either in loco-regional control or in survival could be observed between the two treatment modalities i.e. conventionally fractionated radiotherapy and hyperfractionation. These findings correspond with the results of other authors who were also evaluating the role of hyperfractionation in primary definitive radiotherapy for squamous cell laryngeal carcinoma.

Cummings et al. [22] in their subgroup analysis of the ability of hyperfractionation to conserve the larynx in patients with advanced laryngeal cancer did also not find any significant advantage of hyperfractionation (total dose of 58 Gy/40 fractions/4 weeks, two daily fractions of 1.45 Gy) over conventional fractionation (total dose of 51 Gy/20 fractions/4 weeks, one daily fraction of 2.55 Gy) with respect to local control. They reported the local recurrence free rates at three years of 50% for conventional fractionation and 54% for hyperfractionation (log-rank; P = 0.46).

Antognoni et al. [23] did not demonstrate statistically significant differences in survival according to dose fractionation regimen (conventional vs. accelerated hyperfractionated) in the retrospective analysis of 90 radically irradiated patients with locally advanced laryngeal carcinoma (total dose of 66 Gy with 2 Gy once a day, 5 times a week for conventional fractionation and 1.5 Gy twice a day, 5 times a week for accelerated hyperfractionated radiotherapy).

There was also no statistically significant difference found in five-year survival between hyperfractionation (total dose of 70 to 75 Gy/1.1 Gy in fraction/two daily fractions) and conventional fractionation (total dose of 65 to 70 Gy/2 Gy in fraction, 5 times in week) (p = 0.4) in the study of Tkachev et al. [24] comparing two modalities of radiotherapy of locally advanced tumors (T3N0M0) of the larynx.

On the other hand, the findings of our study are in contrast with the results of Wendt et al. [25]. These authors, reporting the actuarial local control rates above clavicles at two years of 87% in patients with supraglottic larynx when treated with hyperfractionated radiotherapy (total dose of 72 to 79 Gy, two daily fractions of 1.2 Gy), considered this altered fractionation regimen as a possibility for providing improved local control when compared to conventionally fractionated therapy. These results are in general agreement with those of similar studies of hyperfractionation for various head and neck cancers at the University of Florida. In their series, there was an estimated 10% improvement in local control for stage T3 supraglottic laryngeal cancer treated with hyperfractionated radiotherapy when compared to historical controls irradiated with conventional fractionation [26].
The retrospective study of Garden et al. [27] that updated the results of radiotherapy in stage T2 glottic carcinoma showed the five year local control rate for patients treated with twice-daily and once-daily radiotherapy of 79% and 67%, respectively (p = 0.06). According to these authors, although the question of the optimal schedule for patients with Stage T2 disease was left unanswered, patients treated with twice-daily fractionation to a median dose of 77 Gy had an improvement in local control compared with patients treated with 70 Gy in 35 fractions. Similarly, Bignardi et al. [28], reporting the results of hyperfractionated radiotherapy for T2N0 glottic carcinoma at Varese University Hospital, considered the hyperfractionated regimen tested in the study at a very long follow-up as shown to be effective.

Although there are results suggesting that hyperfractionated radiotherapy may offer an acceptable nonsurgical, voice-preserving treatment either for early and advanced laryngeal carcinoma, the review of the literature addressing hyperfractionation in radiotherapy for advanced carcinoma of the larynx still does not show existence of strong arguments for implementation of this fractionation regimen in normally working radiotherapy departments. According to Lee [29], the improved rates of local control for advanced laryngeal cancer treated with primary radiotherapy providing the opportunity for organ preservation could be possibly demonstrated in recent clinical trials with hyperfractionated radiotherapy and concurrent chemoradiotherapy. On the other hand, conformal and intensity-modulated radiotherapy as modern radiotherapy techniques that offer an improvement of the therapeutic ratio by diminishing the incidence of severe acute reactions in normal tissues could be also considered as an excellent possibility for organ preservation in radiotherapy of laryngeal cancer [30, 31].

Conclusion

The absence of statistically significant differences either in loco-regional control or overall survival observed between the two treatment modalities suggested that hyperfractionation regimen was not more efficacious than conventionally fractionated radiotherapy for previously untreated carcinoma of the larynx. These results of our study showing no benefit when accomplishing regimen with two daily fractions for one patient with laryngeal carcinoma, were helpful in the conclusion that there would be no rationale to exploit more intensively the new highly sophisticated equipment in our department using hyperfractionated radiotherapy. In order to provide adequate form and functional organ preservation, as well as increased tumor control probability, we consider 3-D conformal radiotherapy being the cornerstone for the improvement of the outcome in patients with squamous cell carcinoma of the larynx. We also
consider the efforts for the routine use of intensity-modulated radiation therapy in this patients’ category in the near future being strongly recommendable.

REFERENCES


Резиме

ХИПЕРФРАКЦИОНИРАЊЕТО КАКО АЛТЕРИРАН РЕЖИМ НА ФРАКЦИОНИРАЊЕТО БЕО ПРИМАРНАТА РАДИОТЕРАПИЈА КАЈ ПЛАНОЦЕЛУЛУРНИOT КАРЦИНОМ НА ЛАРИНКСОТ

Крстевска В., Смичкоска С.

Целта на студијата беше да се испита ефикасноста на хиперфракционирањето како шема на алтерирана фракционирања третман во споредба со конвенционалното фракционирање во примарната дефинитивна радиотерапија кај ларингеалниот плакоцелуларен карцином. Во периодот од март 1999 до декември 2000 година, 28 пациенти со претходно нелекуван плакоцелуларен карцином на ларинкс беа ирадирани со конвенционално фракционирање со толална доза од 66 до 70 Gy во 33 до 35 фракции/6.5 до 7 недели, 2 Gy/фракција/ден, 5 дена неделно. Од јануари 2001 до јуни 2004, 27 пациенти со истата дијагноза беа проспективно третирани со хиперфракционирање, со радиотерапија остварувана со доза во фракција од 1.2 Gy, два пати дневно, 5 дена во неделата, до толална доза од 74.4 до 79.2 Gy во 62 до 66 фракции 6.2 до 7 недели.

Стапките на комплетниот одговор два месеца по комплетирањето на радиотерапијата изнесуваат 78.6% (22 од 28) и 66.7% (18 од 27) во конвенционално фракционираниот и хиперфракционираниот група, респективно (Fisher exact test; P = 0.246). Двегодишната локорегионална контрола изнесува 61.0% ± 18.1 (95% CI) во конвенционално фракционираниот група и 45.0% ± 18.8 (95% CI) во хиперфракционираниот група (log-rank test; P = 0.075). Двегодишното целосно преживување беше 71.0% ± 16.8 (95% CI) за

конвенционално фракциираната група и 43,0% ± 18,7 (95% CI) за хиперфракциираната група (log-rank test; $P = 0,071$).

Утврденото отсуство на статистички значели неразлики како во локорегионалната контрола, така и во преживувањето меѓу двата модалитети на третман укажа дека хиперфракционарниот режим не беше поефикасен од конвенционално фракционирањето на радиотерапија кај претходно неелекуваниот карцином на ларинксот.

Ключни зборови: карцином на главата и на вратот, ларингеален карцином, радиотерапија, конвенционално фракционирање, хиперфракционирање.

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