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ALTERED FRACTIONATION REGIMENS IN PRIMARY RADIOTHERAPY FOR SQUAMOUS CELL CARCINOMA OF LARYNX, OROPHARYNX AND HYPOPHARYNX – AN ANALYSIS OF PROGNOSTIC FACTORS FOR LOCOREGIONAL CONTROL AND SURVIVAL

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Summary

Detailed evaluation of the most important factors influencing prognosis was one of the objectives of our randomized study comparing altered fractionation schedules with conventional fractionation in primary definitive radiotherapy for squamous cell carcinomas of the larynx, oropharynx and hypopharynx. Conventional fractionation (66 to 70 Gy, 2 Gy per fraction, 5 fractions per week) was performed in 51 of 152 (33.5%) patients, hyperfractionation (74.4 to 79.2 Gy, two fractions of 1.2 Gy per day, 10 fractions per week) in 50 (33.0%) patients, and accelerated fractionation (54 Gy, 1.8 Gy dose per fraction, 5 fractions per week in the basic course and concomitant boost with 1.5 Gy per fraction as a second daily fraction during the last 10 to 12 days) was used in 51 (33.5%) patients. The univariate analysis of six clinical prognostic factors and one histological prognostic factor allowed us to identify the age, Karnofsky index, tumor size (T stage), nodal involvement (N stage), tumor site, and degree of histological differentiation as strongly associated with prognosis. A multivariate analysis was carried out and the size of the tumor (T stage) and the nodal involvement (N stage) were found as two independent variables significantly influencing locoregional control ($p < 0.0008$; $\chi^2 = 11.26$ and $p < 0.00001$; $\chi^2 = 19.58$, respectively). T stage and N stage were also found to be the significant independent prognostic factors for survival ($p < 0.0007$; $\chi^2 = 11.53$ and $p < 0.00001$; $\chi^2 = 33.26$, respectively).

KEY WORDS: *altered fractionation, prognostic factor, head and neck cancer*

REŽIMI ALTERIRANOG FRAKCIONIRANJA U PRIMARNOJ RADIOTERAPIJI KOD PLANOCELULARNOG KARCINOMA LARINKSA, OROFARINKSA I HIPOFARINKSA - ANALIZA PROGNOSTIČKIH FAKTORA LOKOREGIONALNE KONTROLE I PREŽIVLJAVANJA

Sažetak

Detaljna procjena najvažnijih faktora koji utječu na prognozu bolesti bio je jedan od ciljeva naše randomizirane studije u kojoj smo uspoređivali shemu alteriranog frakcioniranja s konvencionalnim frakcioniranjem u primarnoj definitivnoj radioterapiji kod planocelularnih karcinoma larinksa, orofarinksa i hipofarinksa. Konvencionalno frakcioniranje (66 do 70 Gy, 2 Gy u frakciji, 5 frakcija tjedno) provedeno je u 51 od 152 (33,5%) pacijenata, hiperfrakcioniranje (74,4 do 79,2 Gy, dvije frakcije od 1,2 Gy na dan, 10 frakcija tjedno) u 50 (33,0%) pacijenata, i akcelerirano frakcioniranje (54 Gy, 1,8 Gy u frakciji, 5 frakcija tjedno u bazičnom kursu i konkomitantni boost sa 1,5 Gy u frakciji kao druga dnevna frakcija tijekom posljednjih 10 do 12 dana) primijenjeno je u 51 (33,5%) pacijenata. Univarijantnom analizom šest kliničkih prognostičkih faktora i jednog histološkog utvrdili smo da su dob, Karnofsky indeks, veličina tumora (stadij T), nodalna zahvaćenost (stadij N), sijelo i stupanj histološke diferencijacije tumora čvrsto povezani s prognozom. Multivarijantnom analizom utvrđeno je da su veličina (stadij T) i nodalna zahvaćenost (stadij N) tumora nezavisne varijable koje znatno utječu

na lokoregionalnu kontrolu (p<0,0008; 2 = 11,26, odnosno p<0,00001; 2 = 19,58). Stadij T i stadij N također su potvrđeni i kao znakoviti prognostički faktori s obzirom na preživljenje pacijenata (p<0,0007; 2 = 11,53, odnosno p<0,00001; 2 = 33,26).

KLJUČNE RIJEČI: *alterirano frakcioniranje, prognostički faktor, karcinom glave i vrata*

INTRODUCTION

Patients with early stages of squamous cell carcinoma of the larynx, oropharynx and hypopharynx can be treated with surgery or radiotherapy resulting in equal probability for tumor control (1, 2). Locally advanced squamous cell carcinomas of the head and neck are mainly treated with combination of radical surgery and postoperative radiotherapy, although during the last decade, concurrent radiation chemotherapy as a complex treatment strategy appears to be a significant part of organ preservation program in the head and neck region which also results in increasing of 5-year survival rates (3, 4).

The most common treatment failure used to be local and/or locoregional recurrence, stressing the role of the locoregional control in achievement of satisfactory patients' survival. The improvement of the outcome of patients with locally advanced head and neck carcinomas by rational modification of radiation fractionation regimens has been the subject of intensive clinical investigations for more than three decades (5). The two prototypes of altered radiation fractionation regimens are hyperfractionation and accelerated fractionation. Hyperfractionation is based on preferential sparing of late-responding tissues when the radiation dose per fraction is reduced (6). Hyperfractionation allows an escalation of total dose thereby increasing the tumor control rate without increasing the risk of late complications. Accelerated fractionation regimens, which emerged through the recognition that tumor clonogen proliferation occurring during radiotherapy has a detrimental effect on the outcome, are characterized by shortening of the overall treatment time compared with conventional 6 or 7 weeks. Results of large randomized trials addressing the optimization of radiation fractionation show that a number of altered fractionation schedules improve the locoregional control rate but have only modest impact on the overall survival (7, 8). The use of more toxic simultaneous radiochemotherapy protocols and altered fractionated irradiation, as well as the possibility of dose escalation by means of intensity-modulated radiotherapy, enhances the role of the prognostic factors in squamous cell carcinoma of the head and neck (9). These factors could provide identification of high-risk patients, thus enabling better tailoring of therapeutic approach in accordance to the prognosis.

Although the primary aim of our study was to investigate the value of two altered fractionation treatment schedules (hyperfractionation and accelerated fractionation using concomitant boost) in comparison with conventional fractionation, the results showed that no improvement was obtained in locoregional control or in survival. The second but not less important aim of the study was to analyze all the factors possibly influencing the prognosis using the information about patient and tumor characteristics from the created database. By identification of such prognostic factors a more rigorous evaluation of the impact of new treatment strategies in this patient's population would become possible. This could provide selection of patients with unfavorable prognoses for a more aggressive treatment approach and to avoid overtreatment in those with good prognoses.

MATERIAL AND METHODS

From March 1999 to June 2004, 152 previously untreated patients with squamous cell carcinoma of the larynx, oropharynx or hypopharynx were included in a retrospective-prospective study conducted in the Institute of Radiotherapy and Oncology in Skopje. The retrospective part of the study encompassed 51 (33.5%) patients treated from March 1999 until December 2000 using conventionally fractionated radiotherapy. The treatment schedule was 66 to 70 Gy in 6 to 7 weeks (one fraction of 2 Gy

per day, 5 fractions per week). The remaining 101 (66.5%) patients, treated from January 2001 until June 2004, were included in the prospective part of the study and were randomized between two treatment arms (hyperfactionation and accelerated fractionation). Hyperfractionation was performed in 50 (33.0%) patients. The treatment schedule was 74.4 to 79.2 Gy in 6 to 7 weeks (two fractions of 1.2 Gy per day, 10 fractions per week with interfraction interval of at least 6 hr). Accelerated fractionation using concomitant boost was done in 51 (33.5%) patients. The treatment schedule can be summarized as follows: the dose of the basic course, including all sites of disease and electively irradiated areas, was 54 Gy in 6 weeks (daily fraction of 1.8 Gy, 5 fractions per week). The boost, encompassing gross disease only, was given as a second daily fraction of 1.5 Gy during the last 10 to 12 days of the basic course. Total doses ranged from 69 to 72 Gy. The interval between the two daily fractions was 6 hr or more. The relative importance of a number of prognostic factors and of different treatment arms was investigated. The analyzed clinical prognostic factors related to patient were: sex, age and performance status (Karnofsky index). The analyzed clinical prognostic factors related to tumor were: tumor size (T stage), nodal involvement (N stage) and topography of the primary lesion. The degree of histopathological differentiation was analyzed as a histological factor. First, all variables were evaluated by univariate analysis to assess their effect on locoregional control and overall survival. Locoregional control and overall survival have been estimated as a function of time by the Kaplan-Meyer method. The significance of the relation of certain factors with locoregional control and overall survival was tested by the log-rank test (10) and p index. The statistical significance was considered when p value was less than 0.05. The Cox regression model was used to reveal the significance and independence of each prognostic factor (11).

RESULTS

Univariate analysis

Significant factors influencing locoregional control and survival rates were: age, Karnofsky index, tumor size (T stage), nodal involvement (N stage), topography of the primary lesion, and degree of histological differentiation (Table 1 and Table 2).

Age. Patients at the age of 40 years or less had the worst prognosis related to survival ($p<0.05$); the patients at the age of 41 to 70 years had also worse prognosis compared to the group of patients at the age above 70 years ($p<0.05$). The age was not found to be a statistically significant factor with regard to prognosis of locoregional control.

Karnofsky index. The Karnofsky index of 60-70% had a highly unfavorable influence on locoregional control ($p<0.00001$), and also survival ($p<0.00001$) rates.

Tumor size (T stage). Tumor stage was a statistically significant factor with regard to prognosis

Table 1.

UNIVARIATE ANALYSIS FOR LOCOREGIONAL CONTROL

Subgroups	Cases	Locoregional control rates (CI 95%)		p-value
		1 year	2 years	
Sex				
male	137	54.2% ± 8.34	41.1% ± 8.24	ns
female	15	67.2% ± 23.76	50.6% ± 25.30	
Age (years)				
≤ 40	6	33.1% ± 27.65	16.7% ± 19.84	
41-70	128	53.2% ± 8.64	39.4% ± 8.46	ns
>70	18	83.1% ± 17.31	76.5% ± 19.58	
Karnofsky index (%)				
60-70	27	10.8% ± 11.71	0%	< 0.00001
80-100	125	65.3% ± 8.34	51.5% ± 8.76	
T stage				
T1	5	100% ± 0	100% ± 0	
T2	30	97.6% ± 5.48	93.7% ± 8.69	<0.000001
T3	78	59.9% ± 10.88	40.0% ± 10.88	
T4	39	10.4% ± 9.58	0%	
N stage				
N0	71	81.1% ± 9.10	66.3% ± 10.99	
N1	21	90.0% ± 12.83	68.1% ± 19.93	< 0.00001
N2	40	26.6% ± 13.69	7.7% ± 8.26	
N3	20	0%	0%	
Tumor site				
larynx	84	69.1% ± 9.88	57.5% ± 10.57	
oropharynx	49	37.5% ± 13.55	21.5% ± 11.50	< 0.01
hypopharynx	19	40.2% ± 22.05	28.8% ± 20.36	
Differentiation				
good	29	86.2% ± 12.55	71.1% ± 16.50	
moderate	62	68.6% ± 11.55	51.4% ± 12.44	< 0.001
poor	27	11.2% ± 11.89	7.6% ± 9.99	

Table 2.

UNIVARIATE ANALYSIS FOR SURVIVAL

Subgroups	Cases	Survival rates (CI 95%)		p-value
		1 year	2 years	
Sex				
male	137	78.9% ± 6.83	49.7% ± 8.37	ns
female	15	80.3% ± 20.13	40.2% ± 24.81	
Age (years)				
≤ 40	6	82.5% ± 20.4	17.3% ± 20.27	< 0.05
41-70	128	75.2% ± 7.48	47.5% ± 8.65	
>70	18	100% ± 0	75.4% ± 19.90	
Karnofsky index (%)				
60-70	27	33.7% ± 17.83	9.3% ± 10.95	< 0.00001
80-100	125	89.1% ± 5.46	57.6% ± 8.66	
T stage				
T1	5	100% ± 0	100% ± 0	<0.000001
T2	30	100% ± 0	94.7% ± 8.02	
T3	78	86.7% ± 7.53	50.6% ± 11.09	
T4	39	40.2% ± 15.38	3.9% ± 6.08	
N stage				
N0	71	100% ± 0	86.7% ± 7.90	< 0.0001
N1	21	97.5% ± 6.67	70.5% ± 19.50	
N2	40	70.4% ± 14.15	13.4% ± 10.56	
N3	20	4.5% ± 9.08	0%	
Tumor site				
larynx	84	91.2% ± 6.05	63.8% ± 10.28	< 0.001
oropharynx	49	82.6% ± 10.61	35.7% ± 13.41	
hypopharynx	19	53.6% ± 22.42	27.8% ± 20.14	
Differentiation				
good	29	100% ± 0	77.4% ± 15.22	< 0.00001
moderate	62	94.7% ± 5.57	60.6% ± 12.16	
poor	27	40.2% ± 18.49	4.1% ± 7.48	

of locoregional control (p<0.000001, Fig. 1) and survival (p<0.000001). The most negative influence on locoregional control and survival rates had advanced primary lesions (T4). T3 tumors had also demonstrated worse prognosis in comparison with locoregional control and survival rates of T1 and T2 primaries.

Nodal involvement (N stage). Nodal involvement was also a statistically significant factor influencing the prognosis of locoregional control and survival (p<0.00001 and p<0.0001). Locoregional control and survival were significantly worse in

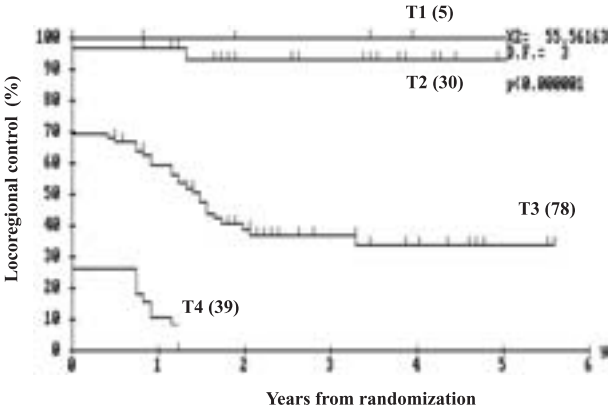

Figure 1. Influence of tumor stage on locoregional control

patients with advanced neck disease (N2 and N3) compared either to patients with clinically negative neck (N0) or to patients having a single metastatic lymph node of less than 3 cm in diameter (N1).

Tumor site. There were significant differences seen in locoregional control and survival rates between the tumors of different origin. Locoregional control and survival were significantly worse for patients with oropharyngeal and hypopharyngeal tumors compared to laryngeal tumors (p<0.01 and p<0.001).

Histology. Low-differentiated tumors had significantly worse prognosis, both in terms of locoregional control and survival (p<0.001 and p<0.00001).

Treatment. Between the three therapeutic arms there was no difference observed, either in terms of locoregional control or in terms of survival.

Multivariate analysis

The significant independent prognostic factors determining locoregional control were the size of the primary tumor (T stage) (p<0.0008; χ^2 = 11.26) and the nodal involvement (N stage) (p<0.00001; χ^2 = 19.58). The significant independent prognostic factors for survival were also T

Table 3.

COX REGRESSION ANALYSIS: INDEPENDENT FACTORS INFLUENCING LOCOREGIONAL CONTROL AND SURVIVAL

Factor	Locoregional control			Survival		
	χ^2	Regression coefficient (β)	p-value	χ^2	Regression coefficient (β)	p-value
T stage	11.26	0.5910	< 0.0008	11.53	0.4988	< 0.0007
N stage	19.58	0.4983	< 0.00001	33.26	0.5977	< 0.00001

stage ($p<0.0007$; $\chi^2 = 11.53$) and nodal involvement (N stage) ($p<0.00001$; $\chi^2 = 33.26$) (Table 3).

DISCUSSION

The carcinoma of the larynx, oropharynx and hypopharynx seems to be predominantly a locoregional disease. Hyperfractionation as an altered fractionation regimen provides improved locoregional control by increasing the total tumor dose, whereas accelerated fractionation is expected to obtain increased level of tumor control probability by counteracting the accelerated tumor clonogen proliferation during irradiation using shortened overall treatment time (12, 13). In this study, there were no differences observed between conventionally fractionated radiotherapy and two variants of altered fractionation irradiation.

The multivariate analysis in this study revealed tumor size (T stage) and nodal involvement (N stage) being significant independent prognostic factors for locoregional control and survival. From the radiobiological point of view, this is a quite obviously expected finding. The probability for tumor eradication, i.e. the probability of achieving complete primary response is inversely related to the number of clonogen tumor cells which increases proportionally with the size of the tumor (14, 15). The advanced stages of laryngeal, oropharyngeal and hypopharyngeal carcinomas are determined by the large size of the primary tumor (T4) and/or advanced neck disease (N2 and N3). In this category of patients, the low locoregional control rates are strongly correlated with the reduced possibility for achieving the complete tumor response by radiotherapy. Also, the poor survival rates in these patients are not related only to the unfavorable locoregional control. The presence of the persistent tumor above the clavicles increases the risk of distant metastases which also negatively influence the prognosis (16).

The prognostic significance of the tumor size and the nodal invasion in terms of both locoregional control and survival has been reported by many other authors (17-21). The great significance of the tumor size and the nodal involvement presented as classic clinical prognostic factors is emphasized by Bourhis et al. (22). The investigated kinetic parameters of the tumor by these authors did not show any significant impact on prognosis instead of the tumor stage and the neck nodal metastases which strongly correlated with both locoregional control and survival. Wendt and Bank (9) also emphasize that in the current clinical practice, T stage and N stage are the most significant prognostic factors involved in the decision for the modality of treatment in patients with squamous cell carcinoma of the head and neck, considering that recently detected biologic factors need extensive clinical testing in prospective trials.

CONCLUSION

In this study, the size of the tumor and the nodal involvement are confirmed to be prognostically highly significant parameters in patients with squamous cell carcinoma of the larynx, oropharynx and hypopharynx. Considering the unfavorable T stage and N stage as the major indicators for unfavorable prognosis and in order to improve the outcome of these patients with advanced disease, we recommend their inclusion into clinical trials investigating the combination of altered fractionation regimens and chemotherapy. We hope that the use of this aggressive treatment may have a potential to improve the outcome of these patients either by increasing the locoregional control of the disease or by decreasing the incidence of distant metastases both possibly leading to an improvement of the overall survival rates.

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