Tumour volume and radiotherapy prolongation in locally advanced head and neck cancer patients treated with radical IMRT

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Aims. The relationship of tumour volume, radiotherapy treatment time and other prognostic factors affecting prognosis was evaluated.

Methods. 184 patients with locally advanced head and neck cancer were treated with radical intensity modulated radiotherapy (IMRT) and compared retrospectively.

Results. In the multivariate analysis the overall survival was dependent on gross tumour volume (GTV), clinical stage (CS), radiotherapy treatment time (RTT) and p16 status. Local control was influenced by GTV, overall RTT and age. DFS was significantly affected by GTV, CS, RTT, p16 status and concomitant chemotherapy (CHT).

Conclusions. The tumour volume and the radiotherapy treatment time were the most significant prognostic factors with the best outcomes in patients with GTV ≤ 55 cc and RTT ≤ 48 days (mean LC 8.1, DFS 7.1 and OS 6.4 years) and worst outcomes with GTV > 55 cc and RTT > 48 days (mean LC 4.4, mean DFS 3.2 and mean OS 2.6 years).

Key words: tumour volume, radiotherapy treatment time, local control, survival, head and neck cancer, IMRT

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INTRODUCTION

Radiation Therapy (RT) is one of the essential treatment methods for squamous head and neck carcinomas (HNC). This is highly effective in these tumours and is indicated as a sole therapy or in combination with surgery, chemotherapy (CHT) and targeted therapy. Factors affecting local control (LC) and overall survival (OS) are related to tumour characteristics (clinical stage, primary tumour location, tumour volume, histology type and grading, HPV status), patient characteristics (age, comorbidity, performance status and smoking and alcohol abuse) and to treatment factors (radiotherapy dose and technique, total radiotherapy duration and concurrent therapies).

Tumour growth rate determines the clinical course of cancer and varies widely among different tumours. It is estimated from volume doubling time (VDT) and results from the balance of the actively dividing cells (the growth fraction in HNC is approximately 20%), cell-cycle time duration and the cell loss (around 90% in HNC) (ref.¹). The mean value for VDT for HNC is 57 days. The potential doubling time is defined as a VDT without any cell loss and for squamous cell cancers (SCC) is approximately 4-5 days. This is the main reason why overall radiation treatment time (RTT) plays a key role in RT of HNC. The probability of local tumour control (TCP) is a func-

tion of random distribution of radiation-induced tumour cell kill and is strongly related to the number of clonogenic tumour cells. The RTT and tumour volume (TV) contribute to the effect of treatment. RTT prolongation has been shown to have deleterious effects on LC and/or OS in many studies on radical RT of SCC. Protocols for compensation of delay in radiotherapy regimens have been developed².

The pre-treatment volumetric analysis is the most important prognostic factor affecting negatively LC and OS increasing the relative risk of 6% per 10 cc difference³. The favourable cut-off Gross Target Volume (GTV) value of 40 cc was estimated in terms of LC (ref.^{4,5}), in the older series the threshold was approximately 100 cc (ref.^{6,7}). Patients could be divided into 3 prognostic groups based on GTV using two volumetric cut-off values 15 and 70 cc (ref.⁸).

The tumour oxygenation is the next well-known prognostic factor in locally advanced HNC (LAHNC). The hypoxic TV was a strong and independent predictor of survival ($P=0.001$) more important than the total TV ($P=0.02$) (ref.⁹). Acute hypoxic stress causes the development of aggressive cancer phenotype with high metastatic rate, resistance to therapeutic agents, and higher tumour recurrence rates¹⁰⁻¹⁴ and it is a major factor of poor outcome^{10,11,14} as proved in numerous clinical trials¹⁵⁻¹⁷. The modification of hypoxia could lead to significant improve-

ment in HNC and uterine cervix cancer¹⁸. Smoking causes more severe hypoxia¹⁹ and is associated with decreased OS after radical RT of HNC (ref.²⁰).

During fractionated radiotherapy hypoxic tumours become oxygenated but at the same time accelerated repopulation occurs if treatment has been prolonged¹ followed by the negative influence on tumour local control and overall survival. Clinical data proved that a one week extension of a curative RT course led to 7–10% loss in LC (ref.¹), the delays of 3 or more days during an accelerated RT of laryngeal tumours (52.5 Gy in 20 fractions in 28 days) resulted in a twice as high local recurrence rate and increased mortality²¹. The negative impact of prolongation in normofractionated radiotherapy in early glottic cancer by 3 or more days worsened 3 times local control in high grade compared to well-differentiated tumours²². The longer RTT had been associated with a higher incidence of distant metastases²³. The role of RTT in the era of chemoradiotherapy (CHRT) is less clear. Prospective randomized trials confirm that the addition of concurrent CHT improved outcome of hyperfractionated definitive RT but do not demonstrate a benefit in the setting of accelerated hypofractionated regimens²⁴.

Intensity modulated radiation therapy with simultaneous integrated boost (SIB) enables proper healthy tissue sparing and improved quality of life (QoL) after curative radiotherapy in HNC (ref.^{25,26}).

We investigated the impact of the prognostic factors (TV and RTT) and the influence on LC, OS and DFS in patients with LAHNC treated with definitive CHRT.

PATIENTS AND METHODS

Patients radically treated with definitive CHRT using the SIB-IMRT technique for LAHNC (stage III or IV) at the Department of Oncology in University Hospital Motol in Prague were analysed retrospectively. The disease staging was evaluated according to UICC TNM classification, 7th edition. Initial staging evaluation consisted of complete medical history including smoking and drinking habits, physical examination and laboratory testing. Dental and nutritional examinations were performed before the RT started. The patients at nutritional risk were offered feeding tube insertion with percutaneous endoscopic gastrostomy (PEG). All patients underwent the initial staging including panendoscopy with biopsies, CT (Computed Tomography) and/or MRI (Magnetic Resonance Imaging) of head and neck region, chest X-ray, abdominal ultrasonography or CT scans of chest and abdomen. FDG-PET/CT (Positron Emission Tomography with the fluoro-deoxyglucose) was a part of the staging as of 2010. Treatment plans were created using a 3D treatment planning system (TPS). Image fusion with diagnostic images was applied to improve target volume delineation. GTV encompassed primary tumour and involved lymph nodes (LN) based on physical exam and imaging studies it was manually contoured and its volume was measured in TPS (treatment planning system). Clinical Target Volume (CTV) included GTV with

5–10 mm margin covering microscopic spread and electively treated LN areas. Planning Target Volume (PTV) was created by adding 5 mm margin to CTV. All patients were treated with the SIB-IMRT technique while immobilized with a thermoplastic mask in the supine position. Moderately accelerated fractionation was used as follows: primary tumour and involved LN (high risk region) received 69.96 Gy in 33 fractions (2.12 Gy per fraction), areas with intermediate risk of subclinical spreading were treated by 61.05 Gy in 33 fractions (1.85 Gy per fraction) and low risk regions were treated electively to 54.12 Gy in 33 fractions (1.64 Gy per fraction)²⁰. Only patients who received the prescribed dose were included in the analysis. Per an internal protocol, unscheduled treatment gaps were compensated by two 6 hours separated fractions in one day whenever feasible. RTT was defined as the time from the first to the last fraction of the RT.

Statistical analysis

The endpoints were LC, DFS and OS. The influence of tumour, patient or treatment related factors on survival was investigated.

LC was defined as the time from the RT start to the last clinical follow-up (in patients with remission) or to the date of local progression of the primary tumour or regional lymph nodes. DFS was defined as the time from the RT start to the last clinical follow-up, local or distant failure, or death. OS was defined as the time from the RT start to the last clinical follow-up or death from any cause.

The data were analysed with statistical software SPSS version 19.0, *P*-values of less than 0.05 were considered significant.

Univariate analyses of survival were carried out by the Kaplan-Meier method and the evaluation of differences between the groups was performed with the log-rank test. Univariate Cox proportional hazards regression analyses were performed to calculate HRs and CIs to evaluate the influence of patient, tumour and treatment characteristics on risk of mortality or recurrence.

A multivariate analyses of endpoints and prognostic factors (with *P*-values < 0.25 from univariate analyses) were performed with the Cox proportional-hazards regression model using forward stepwise method to define the independent contribution of each prognostic factor.

Chi-square test or Student t-test respectively was used for categorical and continuous variables to evaluate differences in risk factors between radiotherapy groups.

RESULTS

Patient characteristics

Data of 184 patients treated during the time period of 2008–2016 with LAHNC stage III and IV were retrospectively evaluated. Their characteristics are listed in Table 1. The majority of patients were men (85%). The mean age was 60.5 years (33–83 years). Patients had newly diagnosed stage III (30% of patients) or IV (70% of patients) SCC of nasopharynx (6%), oropharynx (42%), hypopharynx (22%), larynx (18%) or oral cavity (12%).

Table 1. Patients, tumour and treatment characteristics. Median (range) is reported for continuous and counts (percentage) for categorical variables.

Characteristics	Median (range)
Age (years)	60.5 (33-83)
GTV volume (cc)	55 (5-568)
Radiotherapy treatment time (median, days)	48 (45-80)
Characteristics	Number of patients (%)
Clinical stage III	56 (30)
IV	128 (70)
T1/2	51 (28)
T3/4	133 (72)
N0	31 (17)
N1/N2/N3	153 (83)
Histology grading G1/G2	107 (70)
G3	46 (30)
p16 unknown	165 (90)
negative	7 (4)
positive	12 (6)
Primary tumour site:	
Nasopharynx	11 (6)
Oropharynx	22 (12)
Larynx	34 (18)
Hypopharynx	40 (22)
Oral cavity	77 (42)
Gender - F	28 (15)
- M	156 (85)
Neoadjuvant chemotherapy - no	160 (87)
- yes	24 (13)
Concurrent chemo/bio/radiotherapy	
RT alone	44 (24)
RT + cisplatin	126 (68)
RT + cetuximab	14 (8)
Smokers	141 (77)
Non-smokers	41 (22)
Unknown status	2 (1)
Alcohol abuse - present	111 (60)
- absent	71 (39)
- unknown	2 (1)

Smoking history and a regular alcohol intake was reported by 77% and 60% of patients, retrospectively. The median RTT was 48 days (mean 49 days; range 45-80 days).

The median TV was 55 cc (mean 83 cc; range 5-568 cc).

Median TV was 47 cc in the LC group and 66 cc in the local relapse (LR) group ($P=0.004$). Median TV was 48 cc in the distant metastases free group and 74 cc ($P=0.002$) in the group with present distant metastases occurring in the follow up period.

The mean follow up was 3.3 years (range 0.2-11.6 years). At the time of analysis in April 2020 there were 57 patients alive with median follow up of 6 years (0.2-11.6 years).

Treatment outcomes

The median OS was 2.3 years, median DFS was 4.0 years and mean LC 7.1 years (median was not reached).

The 5-year OS was 33% and 10-years 25%, 5- and 10-year DFS was 49% and 43% and 5- and 10-year LC was 62% and 60% respectively.

LR occurred in 65 patients (35%) and distant metastases (DM) in 43 cases (23%). In 18 cases (10%) there were present both LR and DM at the same time. DM occurred in group with LR in 28% and slightly less in the group with LC in 21% (the difference was not statistically significant).

In the multivariate analysis OS was significantly affected by TV, CS, RTT and p16 status. LC was influenced by TV, RTT and age. DFS was significantly affected by TV, CS, RTT and p16 status and concomitant CHT (Table 2), (Fig. 1, 2).

The TV and RTT were the most significant prognostic factors in the multivariate analysis for OS, DFS and LC. CS and p16 status had significant influence only in OS and DFS. The best prognosis was obtained in patients with $TV \leq 55$ cc and $RTT \leq 48$ days (mean LC 8.1, mean DFS 7.1 and mean OS 6.4 years). Patients with tumours larger than 55 cc and with prolonged RTT over 48 days had the worst outcome (mean LC 4.4, mean DFS 3.2 and mean OS 2.6 years).

Smoking and alcohol abuse was a significant prognostic factor in our series in the univariate but not in the multivariate analyses for LC, DFS and OS.

The age was significant prognostic factor for LC in the multivariate analysis; the older patients have lower risk of local relapse. Patients older than 60 years received significantly less concomitant CHT (68%) than younger patients (84%), $P=0.017$ (Pearson Chi-square test), CS IV and GTV differed non-significantly. In spite of these facts, LC was significantly improved with rising age (DFS and OS was not affected with age). Compared to younger patients, older patients were more often non-smokers (29% vs 15%), which could play the role in prognosis. Women were present more often in the older age group (22% vs 9%).

DISCUSSION

A strong inverse correlation between TV and treatment success was demonstrated. Data on volumetric staging are superior to TNM and AJCC Staging in predicting outcome of HNC treated with curative CHRT (ref.⁸).

We confirmed the prognostic importance of RTT in all tumours irrespective of the volume size, but the worst outcome was found in the large volume group. We confirmed previously published data on the importance of the GTV underestimation in comparison to TNM classification.

Range of GTVs differs widely in published data showing both mean and median volume. In our series the median GTV was 55 cc (mean 83 cc), the others published the median total GTV was 25.8 cc²⁹.

Table 2. Univariate and multivariate Cox proportional hazards regressions analyses for overall survival (OS), loco-regional control (LRC), disease-free survival (DFS).

Prognostic factors	OS univariate		OS multivariate		LC univariate		LC multivariate		DFS univariate		DFS multivariate	
	HR (95% CI), P		HR (95% CI), P		HR (95% CI), P		HR (95% CI), P		HR (95% CI), P		HR (95% CI), P	
Age (years)	1.004 (0.984–1.024), 0.714		NS		0.981 (0.955–1.008), 0.161		0.966 (0.937–0.996), 0.029		0.987 (0.965–1.010), 0.278		NS	
Tumour volume (cc)	1.006 (1.005–1.008), <0.001		1.005 (1.003–1.007), <0.001		1.006 (1.003–1.008), <0.001		1.005 (1.002–1.008), <0.001		1.007 (1.005–1.009), <0.001		1.005 (1.003–1.008), <0.001	
Radiotherapy treatment time days	1.038 (1.007–1.070), 0.017		1.076 (1.019–1.137), 0.008		1.046 (1.008–1.086), 0.018		1.060 (1.006–1.117), 0.029		1.037 (1.001–1.075), 0.041		1.062 (1.008–1.119), 0.024	
Clinical stage (III vs IV)	2.209 (1.444–3.378), <0.001		2.513 (1.439–4.387), 0.001		2.301 (1.228–4.313), 0.009		NS		2.182 (1.298–3.670), 0.003		2.042 (1.069–3.898), 0.031	
T1/2 vs T3/4	1.206 (0.807–1.802), 0.360		NS		1.186 (0.674–2.086), 0.548		NS		1.002 (0.981–1.024), 0.819		NS	
N0 vs N1/N2/N3	1.003 (0.999–1.007), 0.202		NS		2.250 (0.971–5.212), 0.059		NS		1.006 (1.000–1.011), 0.044		NS	
Histology grading G1/G2 vs G3	1.225 (0.794–1.889), 0.358		NS		1.577 (0.850–2.924), 0.148		NS		1.255 (0.762–2.070), 0.372		NS	
p16 unknown vs negative	1.787 (1.021–3.129), 0.042		2.354 (0.976–5.679), 0.057		1.471 (0.695–3.114), 0.313		NS		1.589 (0.773–3.266), 0.208		3.169 (1.349–7.443), 0.008	
unknown vs positive	2.069 (0.979–4.371), 0.057		0.210 (0.055–0.805), 0.023		2.691 (1.063–6.181), 0.037		NS		3.368 (1.442–7.864), 0.005		0.238 (0.062–0.912), 0.036	
Primary tumour site:												
Oropharynx vs Nasopharynx	1.109 (0.502–2.449), 0.799		NS		1.001 (0.302–3.316), 0.999		NS		1.776 (0.822–3.837), 0.144		NS	
Larynx	0.984 (0.595–1.626), 0.948				1.001 (0.492–2.034), 0.999				0.895 (0.482–1.665), 0.727			
Hypopharynx	1.550 (0.988–2.429), 0.056				1.314 (0.692–2.495), 0.404				1.116 (0.631–1.973), 0.706			
Oral cavity	1.458 (0.840–2.531), 0.180				1.779 (0.875–3.618), 0.112				1.636 (0.879–3.045), 0.120			
Gender (F vs M)	1.053 (0.825–1.344), 0.678		NS		0.703 (0.375–1.316), 0.270		NS		1.213 (0.925–1.591), 0.162		NS	
Neoadjuvant chemotherapy (no vs yes)	1.506 (0.923–2.456), 0.101		NS		1.443 (0.735–2.833), 0.287		NS		1.572 (0.920–2.740), 0.111		NS	
Concurrent chemo/bio/radiotherapy												
RT alone vs cisplatin	0.701 (0.472–1.041), 0.078		NS		0.725 (0.422–1.246), 0.245		NS		0.693 (0.436–1.101), 0.120		0.527 (0.323–0.861), 0.011	
RT alone vs cetuximab	0.676 (0.313–1.460), 0.319				0.487 (0.144–1.648), 0.247				0.449 (0.156–1.287), 0.136		NS	
Smokers vs non-smokers	0.617 (0.392–0.971), 0.037		NS		0.698 (0.490–0.993), 0.046		NS		0.651 (0.378–1.120), 0.121		NS	
Alcohol (yes vs no)	0.793 (0.659–0.956), 0.015		NS		0.750 (0.574–0.982), 0.036		NS		0.756 (0.603–0.949), 0.016		NS	

cc, cubic centimetre; CI, confidence interval; DFS, disease free survival; F, women; M, men; GTV, gross tumour volume; HR, hazard ratio; LC, local control; NS, not significant; OS, overall survival; RT, radiotherapy.

Fig. 1. Univariate Kaplan-Meier Analysis proved significantly better local control with gross tumour volume ≤ 55 cc and radiotherapy treatment time ≤ 48 days.

The outcome threshold of the mean GTV predicting local and distant control varies in the published data: 30.5 cc (ref.²⁸), 56.1 cc (ref.²⁹), 58 cc (ref.⁸) and 78 cc (median 70 cc) (ref.³⁰).

Time factor in RT was considered having a weaker prognostic influence in comparison to other well proved factors (e.g. CS, TV, p16 status or drinking and smoking habits). On contrary in our series we found RTT to be the second most important predictor of LC, DFS and OS. Our group of patients was treated with the exact same RT protocol and with a long follow-up period of surviving patients. We conclude that in LAHNC, a length of RTT with association to TV was important statistically significant factor.

The significant factors affecting prognosis in our analysis (CS, TV, p16 status and RTT) confirmed the literature data as expected^{31,32}.

Smoking and alcohol abuse was significant in our series for LC, DFS and OS. TV and RTT was not statistically different between the groups with or without alcohol or smoking abuse and the difference in multivariate analysis is probably associated with much stronger factors affecting prognosis like HPV aetiology³³. The size of TV was not statistically different in p16 positive or negative group, but prognosis was better in the p16 positive tumours in the multivariate analysis.

Favourable LC rates were obtained after definitive RT in patients older than 60 years but chronological age alone is not a reliable indicator of biological condition and should not be an exclusion criterion for curative RT (ref.³⁴).

Improvement of RT results in patients with large tumours is achievable with adopting more strict protocols to maintain RTT including weekend compensations or fast-track programmes³⁵ or with the treatment intensification. Hypoxic regions could be visualised either by MRI (ref.³⁶) or more precisely with PET (ref.³⁷) and the individualized dose escalation confined to the hypoxic TV with the SIB technique may be of potential benefit³⁸.

Another issue to consider is hyperfractionation or

Fig. 2. Univariate Kaplan-Meier Analysis proved significantly increased overall survival according to gross tumour volume ≤ 55 cc and/or radiotherapy treatment time ≤ 48 days.

moderate acceleration in this patient selection⁸ or the use of new regimens with concomitant drugs like hypoxia modifiers¹⁸. On the other hand small TV may have an impact on selecting patients for de-escalation protocols in the future³⁹.

CONCLUSION

The TV and RTT were the strongest independent outcome predictors after curative RT in LAHNC in the multivariate analysis for LC, DFS and OS. Compliance with prescribed fractionation RT regimen and avoiding or minimizing RT prolongation remains one of the most important prerequisites of successful curative treatment of HNC. The best prognosis was defined for patients with TV ≤ 55 cc and RTT ≤ 48 days (mean LC 8.1 years, mean DFS 7.1 years and mean OS 6.4 years). Patients with tumours larger than 55 cc and with prolonged radiotherapy treatment time over 48 days had the worst outcome (mean LC 4.4, mean DFS 3.2, mean OS 2.6 years). Radiotherapy treatment time plays important role irrespective to tumour volume and patients with tumours larger than 55 cc are the probable candidates for radiotherapy intensification protocols (dose escalation, radiotherapy acceleration, hypoxia sensitizer or new concomitant chemotherapy regimen application). Small volume tumours could benefit from treatment de-escalation. Clinical trials with individualized therapy (treatment intensification or dose de-escalation) according to prognostic factors including TV are awaited.

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