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ORIGINAL ARTICLE

# Determining priority risk groups for compensation of treatment breaks in radical radiotherapy in patients with locally advanced head and neck cancer

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## Summary

***Purpose:*** *Prolongation of radiotherapy worsens the results of treatment of head and neck squamous cell carcinoma (HNSCC). The purpose of this study was to identify the prognostic factors most affected by the prolongation of treatment.*

***Methods:*** *184 patients with locally advanced HNSCC were treated with curative chemo-radiation using SIB-IMRT from 2008 to 2016 and the influence of radiotherapy time (RTT) in groups of patients according to prognostic factors was retrospectively evaluated.*

***Results:*** *Median overall survival (OS) was 45 months, median disease-free survival (DFS) was 41 months and median local control (LC) was not reached (mean LRC 68 months). In the multivariate analysis the radiotherapy prolongation negatively affected the LC in stage IV patients, T3/T4, in neck nodes positive disease, in oropharyngeal and oral cavity cancers, after neoadjuvant chemotherapy and in men. The RTT effect on DFS was significant in stage IV patients, patients with neck nodes positive disease and oropharyngeal cancer. RTT prolongation decreased OS within the groups of stage IV and grade 3 tumours.*

***Conclusion:*** *Prolonged RTT was associated with worsened OS and LRC, especially in stage IV patients and/or neck node positive disease and/or oropharyngeal cancer and we recommend that these patients should be prioritized in treatment gap compensation in radical radiotherapy for locally advanced HNSCC.*

***Key words:*** *head and neck cancer, radiotherapy, time factor*

## Introduction

Curative radiotherapy is the main treatment option for locally advanced HNSCC. Factors affecting local control and survival are not only related to tumour characteristics (eg. human papillomavirus or Epstein-Barr aetiology, clinical stage, primary tumour location, type of histology, grading) and patient status (age, co-morbidity, performance status, abuse), but also to treatment factors (radiotherapy dose, fractionation schedule and concurrent chemotherapy or biological therapy with cetuximab).

Radiation treatment time (RTT) prolongation has been shown to have deleterious effects on local tumour control and/or survival in many studies on radical radiotherapy of head and neck cancers, cancers of the uterine cervix, lung cancers, oesophageal cancers, anal squamous cell carcinomas, medulloblastomas and primitive neuroectodermal tu-

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mors (PNETs). Protocols for compensation of delay in radiotherapy regimens have been developed [1].

Treatment time plays a key role in radiation oncology. Various fractionation schemes with shortened RTT like hyperfractionation or accelerated radiotherapy have been evaluated in a multitude of clinical trials in head and neck tumours, unequivocally confirming data from radiobiological experiments with squamous cell tumours. Avoiding radiotherapy prolongation is one of the most effective ways of improving radiation treatment results and treatment gap compensation has thus been a part of standard treatment protocols.

Prolonged RTT has been demonstrated to negatively influence tumour local control and overall survival. Clinical data on head and neck cancers proved that a one week extension of curative radiotherapy course led to 7-10% loss in loco-regional control [2]. Fast tumour repopulation appeared to be the main reason for the negative effect of treatment delays in squamous cell tumours. Patients with glottis tumours suffered worsened local control by 0,32% for every extra day in their radiation schedules [3]. A loss of 0.35 Gy per a day extension has been calculated in early glottis tumour series [4]. Keeping the RTT ≤43 days by rising the single daily fraction to 2.25 Gy led to an improvement in loco-regional control [5]. Unplanned delays of 3 or more days during an accelerated radical radiotherapy of laryngeal tumours (52.5 Gy in 20 fractions in 28 days) resulted in a 2 times higher local recurrence rate and increased mortality [6]. A longer overall RTT had been associated with a higher incidence of distant metastases in a cohort of inoperable head and neck tumours [7].

The role of RTT in the era of chemo-radiation is less clear. Prospective randomized trials confirmed that the addition of concurrent chemotherapy improved the outcome of hyperfractionated definitive radiotherapy but did not demonstrate a benefit in the setting of treatment acceleration [8].

Another time variable, the waiting time from histological diagnosis to the start of radical treatment, has appeared less important. The introduction of multidisciplinary teams helped reduce the time from diagnosis to radical radiotherapy or surgery. Long-term prevention and awareness campaigns are needed to shorten the time from onset of symptoms to diagnosis. Primary prevention of human papillomavirus associated tumours (oropharyngeal cancer) with vaccination has shown promising results [9].

The determination of the acceptable interval from diagnosis to radiotherapy has varied between authors. Days did not play a role, but months of waiting for treatment led to an increase in tumour size and worsening of the clinical stage. The expected reduction of local control in head and neck tumours was calculated in a mathematical model to be 1% for each week of waiting (assuming a 45-day doubling time) [10]. After a median waiting time of 28 days, 62% of patients experienced a 46% increase in tumour volume and 20% developed new lymph node metastases [11].

A Danish study evaluated the significance of the length of time between the onset of the first symptoms, the diagnosis and treatment start, with the median length of this interval being 4.4 months. Each month of delay resulted in a 4.5% decrease in relapse-free survival [12]. In oropharyngeal cancer the median waiting time was 56 days and tumour volume increased during this time in 70% of the cases, resulting in a 16-19% loss of loco-regional control [13]. However, in studies where the waiting intervals were generally shorter, the effect on outcome dissipated. In a cohort of head and neck cancer patients where median waiting time was 44 days no effect on either local control or survival was found [14]. Similarly, in laryngeal carcinoma where the median waiting time to radiotherapy was just 24 days, its association with local relapse was not significant [15].

Another important time factor which can affect treatment outcome in head and neck cancer is treatment package time (TPT) defined as duration between initiation and completion of curative therapy. TPT refers to patient treated with primary surgery and adjuvant chemo-radiotherapy and encompasses both the RTT and time from surgery to radiotherapy initiation. Many studies showed that shorter interval between surgery and radiotherapy improved outcome [16,17]. According to a meta-analysis, adjuvant radiotherapy should be initiated within 6 weeks after radical surgery [18].

In our study we analysed the impact of RTT on local control, overall survival and disease-free survival in patients with locally advanced HNSCC treated by definitive chemo-radiotherapy using accelerated fractionation and IMRT technique.

## Methods

Data of patients with newly diagnosed locally advanced (stage III or IV) HNSCC treated with radical curative radiotherapy using SIB-IMRT technique at the Oncology department of University Hospital were retrospectively evaluated. The disease staging was evaluated according to UICC TNM classification, 7$^{th}$ edition [19]. Initial staging evaluation consisted of complete medical history including smoking and drinking habits, physical examination and laboratory tests. Dental and nutritional examinations were performed before the start of radiotherapy. The patients in nutritional risk were offered

feeding tube insertion with percutaneous endoscopic gastrostomy. All patients underwent initial staging including biopsy, CT and/or MRI of head and neck region, chest X-ray, abdominal ultrasonography or CT scans of chest and abdomen. FDG PET/CT was a part of the staging since 2010. Treatment plans were created using a three-dimensional treatment planning system. Image fusion with diagnostic images (CT with intravenous iodine contrast, MRI and FDG-PET/CT) was applied to improve target volume delineation. Target volumes and organs at risk were contoured on planning CT image in accordance with the ICRU and previously published contouring guidelines [20-23]. Gross tumour volume (GTV) encompassed primary tumour and involved lymph nodes based on physical exam and imaging studies. Clinical target volume (CTV) included GTV with 5-10 mm margin covering microscopic spread and electively treated lymph nodes. Planning target volume (PTV) was created by adding 5 mm margin to CTV. All patients were treated with SIB-IMRT technique using 7 fields with sliding window leaf sequence, while immobilized with thermoplastic mask in supine position on the flat table–top. Moderately accelerated fractionation was used as follows: primary tumour and involved lymph nodes received 69.96 Gy in 33 fractions (2.12 Gy per fraction), areas with high risk of subclinical spreading were treated by 61.05 Gy in 33 fractions (1.85 Gy per fraction) and electively treated areas received 54.12 Gy in 33 fractions (1.64 Gy per fraction). Only patients who received the prescribed dose were included in the analysis. Dose prescription, specification and reporting were performed

**Table 1.** Patients, tumour and treatment characteristics. Median (range) is reported for continuous and counts (percentage) for categorical variables. Statistical difference between groups of radiotherapy was computed using Chi-square test or Student t-test respectively for categorical and continuous variables

| *Variables* | *RT treatment time ≤49 days* *n (%)* | *RT treatment time ≥50 days* *n (%)* | *p value* |
|---|---|---|---|
| Gender | | | 0.974 |
| F | 22 (15) | 6 (15) | |
| M | 123 (85) | 33 (85) | |
| Mean age (years) | 62 (39-83) | 58 (33-80) | |
| Histology grading | | | 0.117 |
| G1/G2 | 84 (69) | 23 (74) | 0.563 |
| G3 | 38 (31) | 8 (26) | |
| Clinical stage | | | 0.404 |
| III | 42 (29) | 14 (36) | |
| IV (non-metastatic) | 103 (71) | 25 (64) | |
| T stage | | | 0.283 |
| T1/2 | 44 (30) | 7 (18) | |
| T3/4 | 101 (70) | 32 (82) | |
| N stage | | | 0.112 |
| N0 | 20 (14) | 11 (28) | |
| N1 | 27 (18) | 4 (10) | |
| N2 | 88 (61) | 20 (52) | |
| N3 | 10 (7) | 4 (10) | |
| Primary tumour site | | | 0.351 |
| Hypopharynx | 31 (21) | 9 (23) | |
| Larynx | 23 (16) | 11 (28) | |
| Nasopharynx | 8 (6) | 3 (8) | |
| Oral cavity | 19 (13) | 3 (8) | |
| Oropharynx | 64 (44) | 13 (33) | |
| Neoadjuvant chemotherapy | | | 0.963 |
| Yes | 19 (13) | 5 (13) | |
| No | 126 (87) | 34 (87) | |
| Concurrent chemo/bio/radiotherapy | | | 0.524 |
| Cisplatin tri-weekly | 63 (43) | 20 (52) | |
| Cisplatin weekly | 37 (26) | 6 (15) | |
| Cetuximab | 10 (7) | 4 (10) | |
| RT alone | 35 (24) | 9 (23) | |

F women; G grade; M men; N nodes; p probability; RT radiotherapy; T tumour.

**Table 2.** Univariate and multivariate Cox proportional hazards regressions analyses of risk factors for whole group for overall survival (OS), local control (LC), disease-free survival (DFS). Only factors significant in univariate analysis were calculated in the multivariate analysis

| *Prognostic factors* | *OS univariate* | *OS multivariate* | *LC univariate* | *LC multivariate* | *DFS univariate* | *DFS multivariate* |
|---|---|---|---|---|---|---|
| | *HR (95% CI), p value* | *HR (95% CI), p value* | *HR (95% CI), p value* | *HR (95% CI), p value* | *HR (95% CI), p value* | *HR (95% CI), p value* |
| Gender (F vs M) | 1.079 (0.834-1.395), p=0.564 | ND | 1.434 (0.748-2.747), p=0.278 | ND | 1.257 (0.958-1.649), p=0.099 | ND |
| Age (years) | 1.001 (0.980-1.022), p=0.947 | ND | 0.977 (0.951-1.004), p=0.094 | ND | 0.989 (0.967-1.012), p=0.359 | ND |
| Overall radiotherapy treatment time (days) | 1.041 (1.009-1.074), p=0.012 | 1.039 (1.007-1.071), p=0.015 | 1.052 (1.013-1.092), p=0.009 | 1.052 (1.013-1.089), p=0.008 | 1.037 (0.999-1.075), p=0.053 | ND |
| Clinical stage (III vs IV) | 2.266 (1.449-3.543), p<0.001 | 2.216 (1.413-3.473), p=0.001 | 2.248 (1.197-4.221), p=0.012 | 2.204 (1.171-4.150), p=0.014 | 2.277 (1.338-3.875), p=0.002 | 2.220 (1.302-3.783), p=0.003 |
| T1/2 vs T3/4 (UICC 7th edition) | 1.210 (0.798-1.834), p=0.369 | ND | 1.289 (0.723-2.300), p=0.390 | ND | 1.099 (0.682-1.769), p=0.696 | ND |
| N0 vs N1/N2/N3 (UICC 7th edition) | 1.359 (0.802-2.304), p=0.238 | ND | 2.208 (0952-5.119), p=0.065 | ND | 1.977 (0.992-3.941), p=0.053 | ND |
| Histology grading G1/G2 vs G3 | 1.234 (0.788-1.932), p=0.358 | ND | 1.584 (0.854-2.937), p=0.144 | ND | 1.302 (0.783-2.165), p=0.310 | ND |
| Primary tumour site | | | | | | |
| Nasopharynx vs Oropharynx | 0.919 (0.414-2.037), p=0.835 | ND | 0.990 (0.297-3.294), p=0.987 | ND | 0.655 (0.290-1.477), p=0.307 | ND |
| Larynx | 0.753 (0.312-1.818), p=0.528 | ND | 1.039 (0.290-3.730), p=0.953 | ND | 0.607 (0.245-1.507), p=0.282 | ND |
| Hypopharynx | 1.414 (0.618-3.236), p=0.412 | ND | 1.296 (0.374-4.491), p=0.682 | ND | 0.729 (0.304-1.753), p=0.481 | ND |
| Oral cavity | 1.264 (0.519-3.078), p=0.606 | ND | 1.811 (0.504-6.502), p=0.363 | ND | 1.065 (0.429-2.645), p=0.892) | ND |
| Neoadjuvant chemotherapy (no vs yes) | 1.633 (0.996-2.676), p=0.052 | ND | 1.443 (0.735-2.836), p=0.287 | ND | 1.552 (0.890-2.708), p=0.122 | ND |
| Concurrent chemo/bio/radiotherapy | | | | | | |
| RT alone vs Cisplatin weekly | 1.382 (0.638-2.996), p=0.412 | ND | 0.933 (0.475-1.831), p=0.840 | ND | 0.904 (0.512-1.595), p=0.727 | ND |
| Cisplatin triweekly | 1.233 (0.559-2.718), p=0.604 | ND | 0.679 (0.373-1.234), p=0.204 | ND | 0.591 (0.356-0.981), p=0.042 | ND |
| Cetuximab | 0.546 (0,0.375-1.679), p=0.546 | ND | 0.532 (0.156-1.806), p=0.311 | ND | 0.450 (0.157-1.290), p=0.137 | ND |

CI confidence interval; DFS disease free survival; F women; G grade; HR hazard ratio; M men; LC local control; N nodes; ND not done; NS not significant; OS overall survival; p probability; RT radiotherapy; T tumour.

according to ICRU 50, 62 and 83 recommendations. RTT was defined as the time from the first to the last fraction of the radiotherapy. Prolonged RTT was defined as ≥ 50 days. Waiting time was defined as the time from biopsy to radiotherapy start.

*Study endpoints*

The endpoints were local control (LC), disease free survival (DFS) and overall survival (OS). The influence of tumour, patient or treatment related factors on survival was investigated.

LC was defined as the time from the radiotherapy start to 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 radiotherapy start to the last clinical follow-up, local or distant failure, or death. OS was defined as the time from the radiotherapy start to the last clinical follow-up or death of any cause.

*Statistics*

The data were analysed with statistical software SPSS version 19.0 and p values<0.05 were considered to indicate statistical significance.

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 analysis of endpoints and prognostic factors with significant p values from univariate analyses were subjected to Cox proportional-hazards regression model using forward stepwise method to define the independent contribution of each prognostic factor.

Fisher's exact test was used to evaluate differences in risk factors between groups.

## Results

*Patient characteristics*

Data of 184 patients treated during 2008-2016 were evaluated. Their characteristics are listed in Table 1. The majority of patients were men (85%). The mean age was 61 years. Patients had newly diagnosed stage III (30% of patients) or IV (70% of patients) squamous cell carcinoma of nasopharynx (6%), oropharynx (42%), hypopharynx (22%), larynx (18%) or oral cavity (12%).

**Table 3.** Univariate and multivariate Cox proportional hazards regressions analyses of the influence of the continuous variable radiotherapy time for overall survival (OS), local control (LC), disease-free survival (DFS) within prognostic subgroups. Only factors significant in univariate analysis were calculated in the multivariate analysis

| *Prognostic factors (subgroups)* | *OS univariate* | *OS multivariate* | *LC univariate* | *LC multivariate* | *DFS univariate* | *DFS multivariate* |
|---|---|---|---|---|---|---|
| | *HR (95% CI), p value* | *HR (95% CI), p value* | *HR (95% CI), p value* | *HR (95% CI), p value* | *HR (95% CI), p value* | *HR (95% CI), p value* |
| Gender | | | | | | |
| F | 1.116 (1.009-1.235), p=0.033 | NS | 1.062 (0.925-1.220), p=0.393 | NS | 1.077 (0.962-1.206), p=0.196 | ND |
| M | 1.035 (0.999-1.072), p= 0.057 | NS | 1.050 (1.008-1.093), p=0.018 | 1.069 (1.026-1.115), p=0.002 | 1.032 (0.991-1.076), p=0.127 | ND |
| Clinical stage | | | | | | |
| Stage III | 1 076 (0.955-1.212), p=0.227 | NS | 0.990 (0.823-1.191), p=0.917 | NS | 0.936 (0.790-1.110), p=0.449 | NS |
| Stage IV | 1.037 (1.005-1.071), p=0.025 | 1.053 (1.007-1.101), p=0.025 | 1.052 (1.014-1,091), p=0,007 | 1.081 (1.038-1.126), p<0,001 | 1.040 (1.005-1,076), p=0,026 | 1.040 (1.005-1.076), p=0.026 |
| T stage (UICC 7th edition) | | | | | | |
| T1/2 | 1.047 (0.987-1.111), p=0.130 | NS | 1.063 (0.980-1.154), p=0.142 | NS | 1.050 (0.979-1.126), p=0.172 | ND |
| T3/4 | 1.037 (1.000-1.076), p=0.049 | NS | 1.047 (1.003-1.093), p=0.034 | 1.076 (1.028-1.127), p=0.002 | 1.033 (0.990-1.078), p=0.135 | ND |

*Continued on the next page*

| *Prognostic factors (subgroups)* | *OS univariate* | *OS multivariate* | *LC univariate* | *LC multivariate* | *DFS univariate* | *DFS multivariate* |
|---|---|---|---|---|---|---|
| | *HR (95% CI), p value* | *HR (95% CI), p value* | *HR (95% CI), p value* | *HR (95% CI), p value* | *HR (95% CI), p value* | *HR (95% CI), p value* |
| N stage (UICC 7th edition) | | | | | | |
| N0 | 1.015 (0.943-1.091), p=0.696 | NS | 0.994 (0.857-1.153), p=0.934 | NS | 0.957 (0.825-1.110), p=0.564 | NS |
| N1/N2/N3 | 1.055 (1.020-1.091), p=0.002 | NS | 1.086 (1.044-1.129), p<0.001 | 1.086 (1.044-1.129), p<0.001 | 1.067 (1.029-1.107), p<0.001 | 1.064 (1.026-1.103), p=0.001 |
| Histology grading | | | | | | |
| G1/G2 | 1.026 (0.951-1.106), p=0.511 | NS | 1.065 (0.970-1.169), p=0.135 | ND | 1034 (0.948-1.128), p=0.452 | NS |
| G3 | 1.067 (1.013-1.124), p=0.014 | | 1.067 (0.993-1.146), p=0.075 | | 1.060 (0.996-1.128), p=0.064 | |
| Primary tumour site: | | | | | | |
| Nasopharynx | 1.254 (0.960-1.638), p=0.097 | 1,057 (1,003-1,113), p=0,038 | 1.163 (0.831-1.627), p=0.379 | ND | 1.218 (0.945-1.570), p=0.129 | ND |
| Oropharynx | 1.053 (1.002-1.106, p=0.042 | NS | 1.100 (1.041-1.162), p=0.001 | NS | 1.074 (1.021-1.129), p=0.006 | NS |
| Larynx | 1.016 (0.940-1.098), p=0.681 | NS | 0.884 (0.721-1.084), p=0.236 | 1,062 (1,000-1,128), p=0,05 | 0.887 (0.742-1.061), p=0.189 | 1,074 (1,021-1,129), p=0,006 |
| Hypopharynx | 1.045 (0.979-1.115), p=0.183 | NS | 1.064 (0.988-1.146), p=0.100 | NS | 1.055 (0.981-1.134), p=0.146 | NS |
| Oral cavity | 1.054 (0.945-1.175), p=0.349 | NS | 1.113 (1.001-1.275), p=0.048 | NS | 1.101 (0.977-1.241), p=0.115 | NS |
| Neoadjuvant chemotherapy | 1.038 (0.999-1.079), p=0.059 | ND | 1.042 (0.995-1.092), p=0.083 | 1.461 (1.118-1.910), p=0.005 | 1.025 (0.977-1.074), p=0.312 | ND |
| No | 1.046 (0.993-1.101), p=0.089 | ND | 1.069 (1.000-1.143), p=0.049 | NS | 1.056 (0.998-1.117), p=0.059 | ND |
| Concurrent chemo/bio/ radiotherapy | 1.091 (0.997-1.193), p=0.057 | ND | 1.091 (0.997-1.193), p=0.057 | 1.069 (1.000-1.143), p=0.049 | 1.089 (0.981-1.208), p=0.109 | ND |
| RT alone vs Cisplatin weekly | 0.994 (0.917-1.078), p=0.889 | ND | 0.994 (0.917-1.078), p=0.889 | ND | 0.990 (0.912-1.075), p=0.815 | ND |
| Cisplatin triweekly | 1.048 (0.993-1.106), p=0.087 | ND | 1.048 (0.993-1.106), p=0.087 | ND | 1.059 (0.988-1.136), p=0.106 | ND |
| Cetuximab | 1.044 (0.976-1.118), p=0.210 | ND | 1.044 (0.976-1.118), p=0.210 | ND | 1.069 (0.987-1.158), p=0.102 | ND |

CI confidence interval; DFS disease free survival; F women; G grade; M men; LC local control; N nodes; ND not done; NS not significant; OS overall survival; p probability; RT radiotherapy; T tumour.

The waiting time varied widely, the mean being 59 days (median 49 days, range 14-206). The minimum length of RTT for applied regimen 69,96 Gy in 33fractions in 6,5 weeks was 45 days. The mean RTT for this regimen was 49 days (median 48 days; range 45-80).

*Treatment outcomes*

In the entire group of patients, the median OS was 45 months, median DFS was 41 months and median LC was not reached (mean LC 68 months). In the univariate analysis every day of radiotherapy prolongation increased the risk of local recurrence with hazard ratio of 1.052 (1.013-1.089), p=0.008 and worsened OS with hazard ratio of 1.041 (1.009-1.074), p=0.012. No significant association was found between the treatment outcome variables and the length of waiting time.

*Factors associated with survival*

In the univariate and multivariate analysis, the following factors were significantly associated with decreased OS: clinical stage IV and prolonged RTT. Factors associated with DFS decline were a higher clinical stage and concurrent chemotherapy. LC was dependent on clinical stage and RTT length in both, univariate and multivariate analysis (Table 2). In the univariate and multivariate analysis, clinical stage and RTT retained significance as predictors of OS. The higher clinical stage was significantly associated with shorter DFS, while LC remained significantly affected by clinical stage and RTT (Table 2).

*Subgroup analysis of RTT effects*

The influence of the RTT prolongation on OS, LC and DFS has been assessed in subgroups of

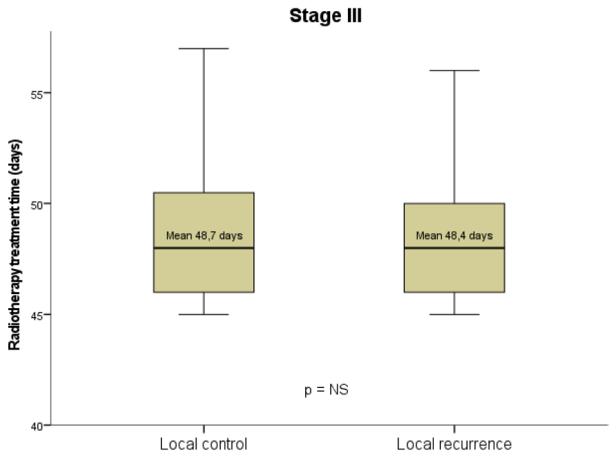


**Figure 1.** The overall radiotherapy treatment time in patients with local control and local recurrence in clinical stage III was not significantly different.

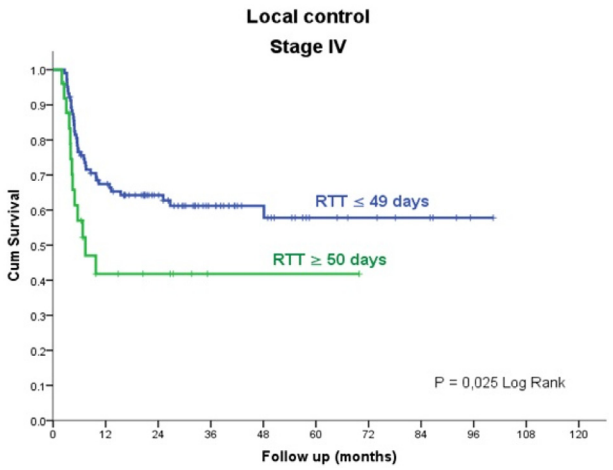


**Figure 3.** Univariate Kaplan-Meier analysis proved significantly improved local control with radiotherapy time ≤ 49 days in clinical stage IV.

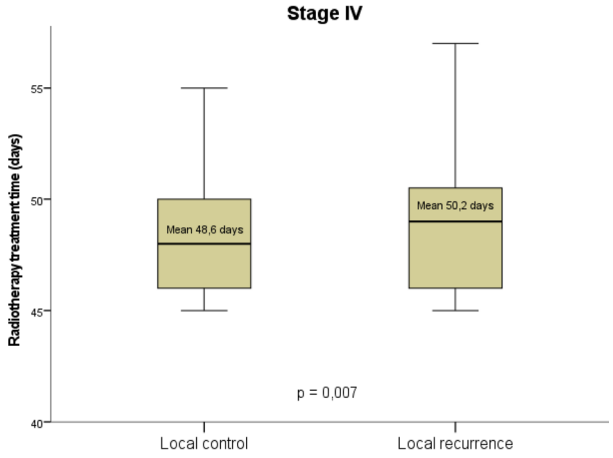


**Figure 2.** Patients with local control in clinical stage IV of disease had significantly shorter overall radiotherapy treatment time.

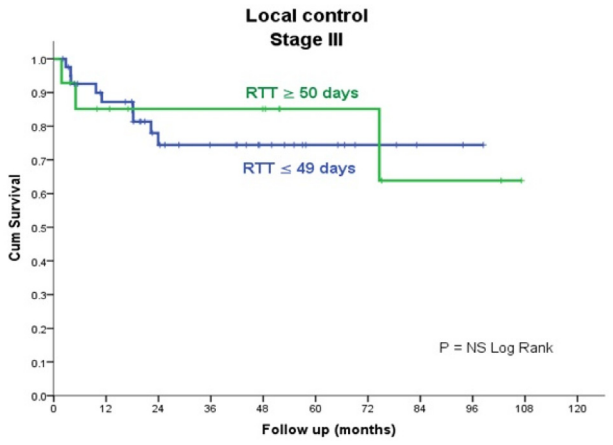


**Figure 4.** Univariate Kaplan-Meier analysis of local control according to overall treatment time in clinical stage III.

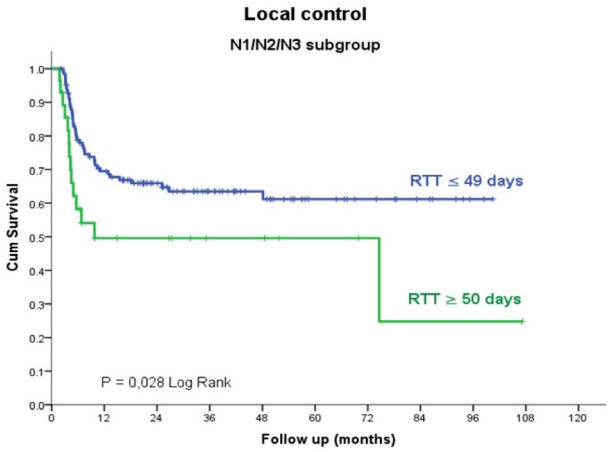


**Figure 5.** Univariate Kaplan-Meier analysis proved significantly improved local control with radiotherapy time ≤ 49 days in neck node positive disease.

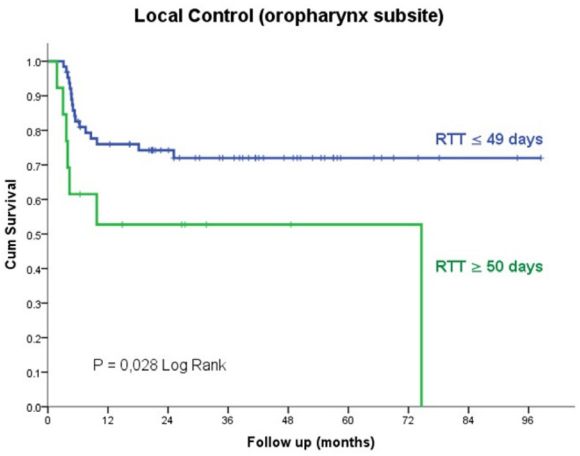


**Figure 7.** Univariate Kaplan-Meier analysis proved statistically significant improvement of local control with radiotherapy treatment time ≤ 49 days in oropharyngeal cancer.

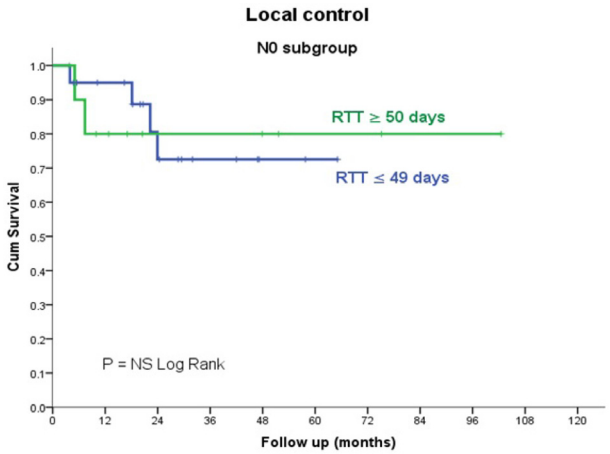


**Figure 6.** Univariate Kaplan-Meier analysis of local control in clinically neck node negative cancer (N0).

patients in univariate and multivariate analysis according to prognostic factors (Table 3). OS was affected by radiotherapy prolongation in subgroups of stage IV patients and in grade 3 tumours. Significant effect on LC was demonstrated in men, in stage IV disease (Figures 1-4), in locally advanced primary tumours T3/4, in neck node positive disease (Figures 5 and 6), in oral cavity and oropharyngeal tumours (Figure 7) and after neoadjuvant chemotherapy. Shorter DFS was significantly linked to prolonged RTT in stage IV or neck node positive disease and in oropharyngeal cancers.

## Discussion

The clinical importance of RTT has been long recognized with ample evidence of its prolongation negatively affecting prognosis and the radiotherapy outcomes. Unscheduled treatment breaks in radiation series may occur as a result of public holidays, radiotherapy machine breakdowns / servicing or due to patient related issues as inter-current diseases, increased radiotherapy and/or chemotherapy toxicities and non-compliance [1]. Detrimental effects of delays during a course of radiotherapy have been emphasized in many studies and a number of compensation methods have been proposed.

In order to define the time factor effect in an inhomogeneous set of head and neck tumours of different locations and stages in the present study, we pooled patients treated with the same radiotherapy protocol and divided them into distinct subgroups based on their baseline characteristics to reveal who benefited the most from adherence to prescribed RTT duration. We identified subgroups of patients and tumours that appeared most vulnerable to consequences of RTT prolongation. Such findings could serve as a tool aiding radiotherapy departments with busy workloads to prioritize patients with the greatest need for treatment gap compensation.

All head and neck squamous cell cancers are negatively influenced with radiotherapy prolongation. In our study it is obvious that more advanced and aggressive tumours have a higher risk of progression upon radiotherapy discontinuation. The strongest factor influenced by the prolonged duration of radiotherapy with respect to LC, DFS and OS is clinical stage IV. The larger the tumour, the more tumour cells that divide during the radiotherapy delay and increase the likelihood of tumour persistence [24].

In our series we demonstrated that time factor affecting local control is more pronounced in men, in advanced stage IV of disease, in locally advanced primary tumour T3/4, in neck node positive disease, in oropharyngeal and oral cavity tumours, after neoadjuvant chemotherapy.

Data on circadian rhythm of cell cycle in mucosa being more pronounced in men than women [25] presuming squamous cell cancers retain some radiobiological properties of healthy tissues from its origin, could explain gender differences in overall RTT effects on LC found in our study.

There have been contradictory accounts of what role may tumour differentiation play in determining the strength of time factor for local control in radiotherapy. The detrimental effects of split-course radiotherapy on LC were observed only in well and moderately differentiated tumours suggesting the ability to accelerate repopulation during treatment prolongation might be lost by dedifferentiation [26]. On the contrary, we previously reported that the impact of radiotherapy prolongation by 3 or more days was most pronounced in poorly differentiated early glottic cancers leading to 3-fold worse local control compared to well differentiated tumours [27]. In the present study of locally advanced head and neck cancers, RTT affected OS in high grade tumours. This association with grading was not significant for the other endpoints of LC and DFS.

The negative effect of prolonged RTT in the neoadjuvant chemotherapy subgroup could be associated with the accelerated clonogenic cells repopulation compared to concomitant chemotherapy, where the overall treatment time enabling accelerated repopulation is shorter [28], even surgery can trigger clonogenic cell repopulation in resectable head and neck tumours [29].

DFS was significantly depended on RTT in stage IV, neck node positive disease and oropharyngeal cancers, but not in other subsites. The influence of overall radiotherapy time on DFS outcomes has been well documented to occur in all HNSCC subsites [30]. The negative impact of prolongation of radiation treatment time in oropharyngeal and oral cavity tumours could be explained with the human papilloma virus aetiology association. These tumours grow faster and rapidly dividing tissues are more sensitive to fractionation and thus overall treatment time becomes more important. Moreover, HPV persistent infection was associated with larger tumour which also affected survival [31]. Due to retrospective evaluation, HPV tumour status was not available in the vast majority of cases in our study.

Notably, no RTT impact on any of the endpoints was detected in subgroups of patients divided based on types of concurrent chemotherapy administration.

## Conclusion

In radiotherapy centres dealing with radical treatment and especially for heavily overloaded units is appropriate to define groups that benefit most from compensating radiotherapy prolongation. Based on our findings, if radiotherapy discontinuation could not be compensated for all patients, patients with stage IV disease and / or positive neck nodal disease and/or oropharyngeal cancer were the most urgent candidates to compensate for treatment gap because the duration of radiotherapy remained an independent prognostic factor for survival and local control in these groups of patients.

## Conflict of interests

The authors declare no conflict of interests.

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