Received:
1 October 2014

Revised:
9 February 2015

Accepted:
16 February 2015

doi: 10.1259/bjr.20140646

Cite this article as:

Nguyen N-TA, Doerwald-Munoz L, Zhang H, Kim D-H, Sagar S, Wright JR, et al. 0-7-21 hypofractionated palliative radiotherapy: an effective treatment for advanced head and neck cancers. *Br J Radiol* 2015;88:20140646.

FULL PAPER

0-7-21 hypofractionated palliative radiotherapy: an effective treatment for advanced head and neck cancers

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This has been presented to the annual meeting of the American Society for Radiation Oncology (Boston, MA, 2012) and to the Multidisciplinary Head and Neck Symposium, Scottsdale, AZ (February 2014).

Objective: We report our experience in providing palliative radiotherapy (RT) to patients with head and neck cancers (HNCs). Our hypofractionated regimen, “0-7-21”, treats patients with 24 Gy in three fractions.

Methods: Patients, disease and response data were retrieved for candidates of 0-7-21 from 2005 to 2012. Primary end points included symptom and tumour size responses to RT based on response evaluation criteria in solid tumours (RECIST) guidelines. Secondary end points included progression-free survival (PFS) within the irradiated field, overall survival (OS) and symptomatic PFS (SPFS), calculated using Kaplan-Meier method and adverse events. Cox proportional hazards regression and logistic regression were used to investigate for prognostic factors.

Results: A total of 110 patients were included. Among the patients, 40% and 31% had complete response for symptoms and tumour size, respectively; 42% and 50%

had partial response for symptoms and tumour size, respectively; and 15% had stability of symptoms and tumour size. Median 6-month OS was 51%, and PFS within the irradiated field was 39%. Planning target volume was predictive of OS ($p < 0.001$), PFS ($p < 0.001$) and SPFS ($p < 0.005$), while higher TNM stage was associated with poorer tumour response ($p = 0.02$).

Conclusion: 0-7-21 is an effective and well-tolerated palliative RT regimen for patients with HNC. There was excellent symptom and local control with acceptable toxicity profile in these patients.

Advances in knowledge: This is the first study to describe the outcomes of 0-7-21 in treating advanced HNCs. The positive results suggest that 0-7-21 provides excellent palliation with minimal toxicity, with significantly less on-treatment time than current published palliative RT regimen.

Head and neck cancer (HNC) is the sixth most common solid malignancy,¹ and the seventh leading cause of cancer death worldwide.² Up to 70% of patients present with locally advanced disease where cure is difficult to achieve.³ In these cases, palliative radiotherapy (RT) is often necessary, as these patients are highly symptomatic from their disease situated at critical locations in the upper aerodigestive tract.

Currently, there is no consensus or guideline for palliative RT for patients with locally advanced HNC, unlike other clinical situations such as for patients with metastatic disease to the bone or brain or even for advanced lung cancer.⁴⁻⁶ There are few retrospective reviews of the diverse schedules of palliative RT in advanced HNC. However, most of these studies use palliative therapy as a synonym

for failed radical therapy. Although longer courses with higher total RT doses have been associated with marginally better outcomes in retrospective reviews,^{7,8} patients not amenable to curative treatments continue to have a dismal prognosis with a median survival of 3–12 months, even with protracted treatments.^{3,7,9,10} Furthermore, delivering an extended course of RT often constitutes a challenge given the poor performance status of these patients. Therefore, the question arose as to whether a shorter course of RT with a high biological effective dose would be more appropriate, assuming it offered satisfactory symptom and disease control.

In our institution at the Juravinski Cancer Centre, a palliative hypofractionated RT regimen, termed “0-7-21”, is

often proposed to patients with advanced incurable and unresectable HNC, especially those with poor performance status and/or multiple comorbidities or evidence of distant metastatic disease. This treatment course consists of three fractions of 8 Gy, given over 3 weeks for a total of 24 Gy. We undertook a retrospective study of our experience, analysing the efficacy of 0-7-21.

METHODS AND MATERIALS

This retrospective study was reviewed and approved by the joint local research ethics committee, the Hamilton Integrated Research Ethics Board. This study was approved by the Hamilton Health Sciences and McMaster University Research Ethics Board.

Patients

We identified 178 patients who were treated between January 2005 and December 2012 with 0-7-21. The inclusion criteria were:

- (1) patients aged 18 years and older
- (2) biopsy proven primary HNC
- (3) patients deemed unsuitable for radical treatments owing to significant comorbidities, poor performance status, unresectable tumour, distant metastatic disease or prior radical RT at the same site as the current tumour.

Patients were excluded if they:

- (1) did not have any follow up after completion of treatments
- (2) received only one fraction of RT out of the three planned fractions
- (3) underwent chemotherapy or surgery for the same tumour within 3 months of 0-7-21.

Patients were staged according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging manual.¹¹ The treatment decision for palliative RT as a single modality was made in the multidisciplinary HNC clinic of the Juravinski Cancer Centre, Hamilton, ON, Canada, between healthcare professionals and the patient.

The patients' characteristics, including most prominent presenting symptoms, stage and Eastern Co-operative Oncology Group (ECOG) performance status¹² were retrieved from the patients' charts. Data pertaining to outcomes were also extracted from the patients' paper and electronic charts. The age-adjusted Charlson comorbidity index (CCI)^{13,14} was calculated using comorbidities retrieved as part of the chart review.

Age-adjusted Charlson comorbidity index

The age-adjusted CCI^{13,14} is a widely used index and has been validated for patients with HNC.¹³ It contains 19 different medical conditions, each weighted 1–6, according to its potential impact on mortality, for a possible total score of 0–37. To account for the effects on mortality of increasing age, one additional point can be added to the CCI for each decade above 50 years old. The CCI is designed to stratify patients in order to control for the confounding influence of comorbid conditions on overall survival (OS).

End points evaluation

The primary end points of the study were defined as responses to RT in terms of (1) symptom and (2) tumour size. These

responses within the irradiated field were stratified into complete response (CR), partial response (PR), stable disease (SD) and progression of disease (PD) based on the response evaluation criteria in solid tumours (RECIST) 1.0 guideline.¹⁵ CR was defined as clinical disappearance of all target lesions within the irradiated field. PR was defined as a decrease of at least 30% of the size of the tumour, as measured in its largest axis. PD corresponded to an increase of at least 20% of the size of the target disease. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase of the target lesions to qualify for PD. Tumour size responses were based on clinical or radiological assessment, depending on the subsites of HNC treated. In the case of a differential response, the lesser response was reported. From a symptomatic perspective, CR was defined as complete resolution of symptoms, PR as some symptomatic improvement, SD as no symptomatic improvement, PD as worsening of symptoms.

The secondary end points included the symptomatic progression-free survival (SPFS), progression-free survival (PFS) within the irradiated field, OS and significant adverse events (AEs) according to the Common Terminology Criteria for Adverse Events v. 4.0 scale.^{16,17} PFS within the irradiated field was calculated from the start date of RT to the date of clinical or radiological recurrence within the irradiated field, whichever occurred first. SPFS was determined using the start date of RT to the date of symptomatic recurrence. OS was defined as the start date of RT to the date of death or the date of last follow-up. The dates and causes of death were retrieved in the electronic and paper charts and correlated with the Cancer Care Ontario database.

Finally, an exploratory analysis was also carried out to determine factors associated with higher and longer responses.

0-7-21 radiotherapy

Patients receiving 0-7-21 RT regimen underwent three fractions of 8 Gy each, for a total of 24 Gy. The first treatment was given on Day 0; the second treatment was given on Day 7; and the third and final treatment was given on Day 21. Patients were immobilized in a supine treatment position in a custom mask manufactured in the mould room. Most patients underwent simulation and standard intensity-modulated RT (IMRT) planning. The clinical tumour volume (CTV) included all regional gross disease (primary tumour and/or regional nodal disease). The planning target volume (PTV) included the CTV with an additional margin of 0.5–1.0 cm. Some patients with more superficial skin lesions had clinical planning for which the radiation field encompassed the gross disease (primary tumour and/or nodal disease) with at least a 1.5-cm margin. Surface bolus was used for disease with skin invasion and/or fungation. Techniques of RT such as CT image-based IMRT, three-dimensional (3D) conformal RT or simple direct fields were used at the discretion of the treating physician. The spinal cord dose was limited to 16 Gy.

Follow-up

At each follow-up visit, medical history and routine head and neck examination were performed, including flexible nasopharyngolaryngoscopy when indicated. Patients were seen prior

to the second and third fractions of RT, to assess for any AEs related to the treatment and to manage any treatment- or disease-related supportive needs. The first follow-up appointment after completion of RT was at 6–8 weeks post RT. Thereafter, patients were followed every 3 months, earlier/more frequently if symptoms or concerns arose in the interim and/or were discharged from the clinic when too unwell to continue follow-up. Patients with PD or SD after completion of treatments were treated with best supportive care.

Statistical analysis

Descriptive statistics were used to summarize the patients' characteristics and outcomes. Time-to-event outcomes, such as OS, PFS within the irradiated field and SPFS, were estimated using the Kaplan–Meier method. Cox proportional hazards regression and logistic regression were used to investigate whether selected factors were prognostic of time-to-event outcomes and having an objective tumour response, respectively. All factors were evaluated using univariable analyses; no multivariable model was constructed owing to the lack of significance observed on univariable analyses (excluding PTV). All tests were two-sided, and a $p \leq 0.05$ was considered statistically significant. No corrections for multiplicity were applied. All analyses were performed in SAS® v. 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Patient population

Between 2005 and 2012, 178 identified patients with HNC were deemed unsuitable for definitive treatment with any combination of surgery, chemoradiotherapy (CRT) or radical RT, and were thus planned for 0-7-21. Of these 178 patients who met the inclusion criteria, 68 patients were excluded. Excluded patients included 10 patients who received 1 fraction of RT only, owing to overwhelmingly poor pre-treatment functional status, personal choice or death unrelated to treatments; 23 lacked follow-up notes; 8 received additional RT; 9 had RT post-operatively and thus not for symptom palliation; 17 had had chemotherapy for the same tumour within 3 months of RT; and 1 underwent surgery within 3 months of RT. A total 110 patients were included in the final analysis.

Patients' and tumour characteristics are included in Table 1. The median PTV for those treated with 3D conformal RT and IMRT was 275 cm² (range, 168–458 cm²).

Outcomes

Symptom and tumour size response

At the time of analysis, 88 (80%) patients had died. The median follow-up was 5.58 months (range, 0.66 months–8.18 years). Symptom and tumour size responses are reported in Table 2. Of note, three (3.2%) patients were asymptomatic prior to RT, and thus symptom responses were not recorded for them. An example of the most common response, PR, is illustrated in Figure 1a,b.

SPFS, PFS within the irradiated field and OS

The median SPFS was 3.9 months [95% confidence interval (CI), 3.3–6.0]. The median PFS within the irradiated field was

Table 1. Patients and tumour characteristics

Patients (<i>n</i> = 110)	<i>n</i> (%)
Age (years), median (range)	77.3 (45–98)
Gender	
Males	68 (61.8)
Females	42 (38.2)
Disease subsites	
Oral cavity	25 (22.7)
Oropharynx	20 (18.2)
Larynx	13 (11.8)
Hypopharynx	9 (8.2)
Skin squamous cell carcinoma	20 (18.2)
Parotid	4 (3.6)
Unknown primary	5 (4.5)
Merkel/melanoma	9 (8.2)
Nasopharynx, sinus, thyroid	5 (4.5)
Patients with recurrent disease	23 (21)
Prior local treatment	
Surgery	15 (13.6)
Radiotherapy	3 (2.7)
Cryosurgery	1 (0.9)
Stages of disease	
II	15 (13.6)
III	27 (24.5)
IV	68 (61.8)
Predominant symptom	
Dysphagia	34 (30.9)
Pain	55 (50.0)
Ulceration	12 (10.9)
Hoarseness	3 (2.7)
Others	3 (2.7)
No symptom	3 (2.7)
Age-adjusted Charlson comorbidity index, median (range)	5 (0–16)
<i>n</i> (%) ≥ 6	50 (45.5)
Eastern Co-operative Oncology Group performance status	
1	41 (37.3)
2	27 (24.5)
3	42 (38.2)

3.8 months (95% CI, 3.2–5.1). The actuarial 6-month and 12-month PFS within the irradiated field was 39% and 29%, respectively (Figure 2). The median OS was 6.2 months (95% CI, 4.45–8.02). The actuarial 6-month and 12-month OS was 50.7% and 26%, respectively (Figure 3). 71 (64.5%) patients

Table 2. Overall survival (OS), progression-free survival (PFS) within the irradiated field, symptomatic PFS (SPFS) and symptom and tumour responses to 0-7-21 radiation

Outcomes evaluated	Values
Median follow-up (range)	5.58 months (0.66 months–8.18 years)
Tumour response, <i>n</i> (%)	
CR	34 (30.9)
PR	56 (50.9)
SD	17 (15.5)
PD	3 (2.7)
Symptom response, <i>n</i> (%)	
CR	44 (40.0)
PR	46 (41.8)
SD	17 (15.5)
PD	0 (0%)
Median OS (months) (95% CI)	6.2 (4.45–8.02)
6-months OS (%)	50.7
12-months OS (%)	26
Median PFS (months) (95% CI)	3.8 (3.2–5.1)
6-months PFS (%)	39
12-months PFS (%)	29
SPFS, median (months) (95% CI)	3.9 (3.3–6.0)
6-months SPFS (%)	40.0

CI, confidence interval; CR, complete response; PD, progression of disease; PR, partial response; SD, stable disease.

died from their disease, and 16 (14.5%) died from other causes (Table 2). No patient underwent further local treatment after 0-7-21.

Adverse events related to treatments

Two (2.1%) patients died during their therapy, but owing to causes unrelated to treatments. Nine (9.5%) patients received two out of three scheduled fractions (16 Gy); two patients required interruption of treatments owing to complications of RT, four patients because they felt they could not tolerate further treatments and three patients owing to deterioration of overall performance status. Three (3.2%) patients required admission during treatments, including one owing to grade 3 mucositis (1%). Overall ECOG performance status did not change significantly ($p > 0.05$) at the first follow-up after completion of 0-7-21 for most patients. None of the patients required feeding tube insertion owing to toxicities of RT.

Prognostic factors for PFS within the irradiated field, SPFS and degree of tumour response

On univariate analysis, only PTV was a statistically significant predictive factor for OS [hazard ratio (HR) = 1.38; 95% CI, 1.19–1.60; $p < 0.001$], PFS within the irradiated field (HR = 1.25;

95% CI, 1.11–1.41; $p < 0.001$) and SPFS (HR = 1.21; 95% CI, 1.06–1.37; $p < 0.005$). Higher TNM stage was associated with poorer tumour response (odds ratio = 0.52; range, 0.30–0.90; $p = 0.020$) (Table 3).

Figure 1. CT scan of the neck of a patient with right tonsillar cancer with nodal metastases: (a) pre 0-7-21 and (b) 3 months post 0-7-21.

(a)

(b)

DISCUSSION

This review was undertaken because there is still limited data regarding the optimal RT dose fractionation and treatment-induced toxicity for palliation of HNCs.¹⁸ Our results suggest that 0-7-21 can effectively provide symptomatic and local

Figure 2. Progression-free survival within the irradiated field.

control for a meaningful period of time in patients with advanced HNC, deemed incurable.

From a radiobiological perspective, limiting the overall treatment time is known to lead to increased tumour cell kill¹⁹ and improved outcomes in HNC.^{20–22} Although theoretically it may be associated with increased late side effects,²³ in more recent studies, this potentially high incidence of tissue complications has not been appreciated yet.^{24,25} We chose a hypofractionated radiation scheme, as it provides an effective dose within a short overall treatment time. It has also been reported that increasing the dose of RT is associated with a higher treatment response and OS.²⁶ However, in view of the relatively short median survival in this population, the practical importance of length of treatment cannot be overstated among patients with advanced or metastatic HNC²⁷ and must be balanced with symptomatic relief and local disease control.

The majority of patients (81.8%) experienced both symptomatic and objective tumour response (CR and PR) with 0-7-21. This is comparable with multiple other palliative regimens, while requiring less treatment time. For example, the “QUAD SHOT” palliative RT regimen by Corry et al⁷ of 14 Gy in four fractions, which may be repeated up to two times every 4 weeks provided PR or CR in 53% of patients. Furthermore, in the study by Al-mamgani et al,²³ which included 158 patients treated with 50 Gy in 16 fractions, the overall response rate was 73%, and the subjective response rate was 57%. Finally, in the study by Mohanti et al³ where patients received 20 Gy in five fractions and 30% of patients underwent further RT, up to 70 Gy, the response rate ranged from 89% to 96%, depending on the symptoms assessed.

Of note, Stevens et al²⁶ reviewed the results of their palliative RT, which included most frequently a split-course regimen, that is, two cycles of 25 Gy in ten fractions given over 2 weeks, separated by a 2-week break. The RT dose, pathological type, and positive treatment response were predictive of modest OS benefits ($p < 0.01$ for both). However, it was difficult to reliably assess its effectiveness specifically in palliating symptoms, which is arguably the most important end point in this population, as symptoms were recorded in only 65% of the treated patients. Furthermore, contrary to the patients in the aforementioned study, most of the patients in our cohort would not likely have been able to withstand a more prolonged course of RT, given their poor pre-RT performance status.

In our cohort, the median SPFS was 3.68 months, PFS within the irradiated field was 3.63 months and OS was 6.2 months. More importantly, 0-7-21 provided disease and symptom control for a median of 59% of the remaining lifetime of patients. This was comparable to the report by Corry et al⁷ where the disease was controlled for a median of 54% of the remaining lifetime of patients.

It is important to note that the OS from some studies was slightly higher than for this present cohort. For example, the median OS was 17 months in Al-mamgani’s report. One possible explanation is that our patients had a higher age-adjusted CCI and poorer ECOG performance status, both factors known to negatively impact survival. In fact, in Al-mamgani’s cohort, up to 10% of patients were well enough to receive chemotherapy, while all our patients were deemed unfit for any radical course of RT, let alone systemic therapy. Thus, their patients may have had a better performance status and/or

Figure 3. Overall survival.

Table 3. Univariate analysis for prognostic factors of overall survival (OS), progression-free survival (PFS) within the irradiated field and symptomatic PFS (SPFS)

Prognostic factors	OS, HR (95% CI) (<i>p</i> -value)	PFS, HR (95% CI) (<i>p</i> -value)	SPFS, HR (95% CI) (<i>p</i> -value)
Age (years)	0.99 (0.98–1.01) (0.53)	0.99 (0.97–1.01) (0.35)	1.00 (0.98–1.02) (0.85)
Age-adjusted Charlson comorbidity index	0.93 (0.87–1.00) (0.066)	0.93 (0.87–1.00) (0.05)	0.96 (0.89–1.03) (0.29)
Stage	1.29 (0.95–1.77) (0.11)	1.26 (0.93–1.69) (0.13)	1.11 (0.82–1.50) (0.52)
Eastern Co-operative Oncology Group performance status	0.96 (0.76–1.21) (0.71)	0.95 (0.76–1.19) (0.66)	0.86 (0.68–1.10) (0.22)
Radiation dose (1600 cGy)	1.90 (0.95–3.81) (0.071)	1.85 (0.92–3.70) (0.083)	1.76 (0.81–3.84) (0.16)
Planning target volume ^a (cm ³)	1.38 (1.19–1.60)* (<0.001)	1.25 (1.11–1.41)* (<0.001)	1.21 (1.06–1.37)* (<0.005)

CI, confidence interval; HR, hazard ratio.

^aStatistically significant prognostic factor.

lower age-adjusted CCI than those in our cohort, allowing them to be candidates for systemic treatments. In addition, their disease may have had a longer response owing to the known synergistic effect of CRT in the treatment of HNCs. Finally, a higher proportion of their cohort had oropharyngeal and laryngeal cancers, which are known to respond particularly well to RT.

Statistical analysis was also carried out to determine prognostic factors for response. In patients who were planned with a CT scan and with a recorded PTV, the larger PTV was associated with statistically significantly shorter OS (HR, 1.38; range, 1.19–1.60; $p < 0.001$), PFS within the irradiated field (HR, 1.25; range, 1.11–1.41; $p < 0.001$) and SPFS (HR, 1.21; range, 1.06–1.37; $p < 0.005$). These findings are in concordance with other studies of patients with advanced HNC treated with RT or CRT, where higher tumour volume was associated with poorer OS, PFS and locoregional control.^{28,29} This correlation between OS and tumour volume was stronger than that of OS and the AJCC staging system, most likely because malignant lesions are irregularly shaped or sized; thus, a three-dimensional approach provides a better representation of the true tumour burden.

In our analysis, a higher CCI was associated with mildly improved survival, which was likely related to some limitations of the CCI calculations. It did not account for the staging of the primary HNC, unless distant metastases were present,³⁰ which is one of the main determinants of patients OS. Furthermore, our population's median OS was less than 6 months, and it is known that the CCI has a reduced predictive ability for outcomes of less than 6 months.³⁰ Therefore, in our study, CCI was calculated primarily to highlight the numerous comorbidities of our patients, indicating their general poor prognosis owing to factors other than their HNC rather than to predict patients' outcomes.

From our data, there was no statistically significant association between the RT doses (16 Gy compared with 24 Gy) and outcomes. This may be related to the fact that the subgroup receiving 16 Gy was too small to detect a small difference in

PFS within the irradiated field, SPFS and degree of tumour response.

Finally, 0-7-21 was well tolerated by most patients. Only three patients required hospital admissions, including one who refused hospitalization prior to initiation of RT. There was no significant change in the performance status, no feeding tube insertion or death owing to 0-7-21. There was minimal grade 3 or above mucositis, dermatitis or xerostomia, likely because the irradiated volumes remained relatively moderate in size, in addition to time between fractions allowed some normal tissue healing. This is an important result since toxicities from treatments should be minimal when given with a palliative intent.

The limitation of our study comprised its retrospective nature. There was no consistent use of standardized quality of life evaluation and thus, quantification of improvement of quality of life was not possible for our cohort. This is, however, a common occurrence and similar to other studies reporting outcomes of palliative RT for patients with HNC.^{3,26,27,31,32} Furthermore, it was difficult for many patients to come to follow-up appointments because of their poor performance status, distance from the cancer centre or their care being transferred to a palliative care or family physician. It is possible that in some patients, disease recurrence or worsening of symptoms occurred earlier than reported. This is a challenge encountered in all retrospective series, especially those dealing with palliation.

CONCLUSION

In conclusion, our hypofractionated RT regimen 0-7-21 with a dose of 24 Gy in three fractions is an effective palliative schedule for controlling symptoms and disease in patients with advanced HNC deemed unsuitable for curative treatment options. Even in patients with moderate-to-poor performance status, there were symptom and tumour responses in most patients, similar to other published series. Most importantly, patients had disease and symptom control for 59% of their remaining lifetime, with less treatment time. In view of the relatively short median survivals in this population, 0-7-21 appears to be a highly effective palliative treatment option for

these patients, which may improve the quality of their remaining life. A prospective Phase II trial is currently underway to better quantitate the magnitude of clinical and radiological improvement. As we proceed with an agenda of improving outcomes for our HNC patients, Phase III trials are our ultimate goal. Challenges such as the most appropriate RT

prescription for a standard arm, and the role of chemotherapy remain.

ACKNOWLEDGMENTS

Gregory Pond, MSc, PhD, for his continual support for the statistical analyses.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74–108.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893–917. doi: [10.1002/ijc.25516](https://doi.org/10.1002/ijc.25516)
3. Mohanti BK, Umapathy H, Bahadur S, Thakar A, Pathy S. Short course palliative radiotherapy of 20 Gy in 5 fractions for advanced and incurable head and neck cancer: AIIMS study. *Radiother Oncol* 2004; **71**: 275–80.
4. Fairchild A, Harris K, Barnes E, Wong R, Lutz S, Bezjak A, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. *J Clin Oncol* 2008; **26**: 4001–11. doi: [10.1200/JCO.2007.15.3312](https://doi.org/10.1200/JCO.2007.15.3312)
5. Toy E, Macbeth F, Coles B, Melville A, Eastwood A. Palliative thoracic radiotherapy for non-small-cell lung cancer: a systematic review. *Am J Clin Oncol* 2003; **26**: 112–20.
6. Rodrigues G, Videtic GMM, Sur R, Bezjak A, Bradley J, Hahn CA, et al. Palliative thoracic radiotherapy in lung cancer: an American Society for Radiation Oncology evidence-based clinical practice guideline. *Pract Radiat Oncol* 2011; **1**: 60–71.
7. Corry J, Peters LJ, Costa ID, Milner AD, Fawns H, Rischin D, et al. The “QUAD SHOT”—a phase II study of palliative radiotherapy for incurable head and neck cancer. *Radiother Oncol* 2005; **77**: 137–42.
8. Browman GP, Levine MN, Hodson DI, Sathya J, Russell R, Skingley P, et al. The head and neck radiotherapy questionnaire: a morbidity/quality-of-life instrument for clinical trials of radiation therapy in locally advanced head and neck cancer. *J Clin Oncol* 1993; **11**: 863–72.
9. Gibson MK, Li Y, Murphy B, Hussain MH, DeConti RC, Ensley J, et al; Eastern Cooperative Oncology Group. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2005; **23**: 3562–7.
10. Kowalski LP, Carvalho AL. Natural history of untreated head and neck cancer. *Eur J Cancer* 2000; **36**: 1032–7.
11. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC cancer staging handbook: from the AJCC cancer staging manual*. 7th edn. New York, NY: Springer Science; 2010.
12. Zubrod CG, Schneiderman M, Frei E III, Brindley C, Gold GL, Shnider B, et al. Appraisal of methods for the study of chemotherapy in man: comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *J Chronic Dis* 1960; **11**: 7–33.
13. Singh B, Bhaya M, Stern J, Roland JT, Zimble M, Rosenfeld RM, et al. Validation of the Charlson comorbidity index in patients with head and neck cancer: a multi-institutional study. *Laryngoscope* 1997; **107**: 1469–75.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–83.
15. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205–16.
16. Services USDoHaH. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. 2009. [Updated 5 May 2014; cited 1 October 2014.] Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
17. Institute NIOH-NC. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. [Updated 14 June 2010; cited 1 October 2014.] Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
18. Hodson DI, Bruera E, Eapen L, Groome P, Keane T, Larsson S, et al. The role of palliative radiotherapy in advanced head and neck cancer. *Can J Oncol* 1996; **6**: 54–60.
19. Joiner M, van der Kogel A. *Basic clinical radiobiology*. 4th edn. London, UK: Edward Arnold; 2009.
20. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al; Meta-Analysis of Radiotherapy in Carcinomas of Head and Neck (MARCH) Collaborative Group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet* 2006; **368**: 843–54.
21. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000; **48**: 7–16.
22. Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet* 2003; **362**: 933–40.
23. Al-mamgani A, Tans L, Van rooij PH, Noever I, Baatenburg de jong RJ, Levendag PC. Hypofractionated radiotherapy denoted as the “Christie scheme”: an effective means of palliating patients with head and neck cancers not suitable for curative treatment. *Acta Oncol* 2009; **48**: 562–70. doi: [10.1080/02841860902740899](https://doi.org/10.1080/02841860902740899)
24. Nieder C, Milas L, Ang KK. Tissue tolerance to reirradiation. *Semin Radiat Oncol* 2000; **10**: 200–9.
25. Datta NR, Nagar YS, Singh S, Naryan L. Loco-regional failures in head and neck cancer: can they be effectively salvaged by nonsurgical therapeutic modalities? *Int J Clin Oncol* 2003; **8**: 31–9.
26. Stevens CM, Huang SH, Fung S, Bayley AJ, Cho JB, Cummings BJ, et al. Retrospective study of palliative radiotherapy in newly diagnosed head and neck carcinoma. *Int J Radiat Oncol Biol Phys* 2011; **81**: 958–63. doi: [10.1016/j.ijrobp.2010.06.055](https://doi.org/10.1016/j.ijrobp.2010.06.055)

27. Chen AM, Vaughan A, Narayan S, Vijayakumar S. Palliative radiation therapy for head and neck cancer: toward an optimal fractionation scheme. *Head Neck* 2008; **30**: 1586–91. doi: [10.1002/hed.20894](https://doi.org/10.1002/hed.20894)
28. Lok BH, Setton J, Caria N, Romanyshyn J, Wolden SL, Zelefsky MJ, et al. Intensity-modulated radiation therapy in oropharyngeal carcinoma: effect of tumor volume on clinical outcomes. *Int J Radiat Oncol Biol Phys* 2012; **82**: 1851–7. doi: [10.1016/j.ijrobp.2011.03.029](https://doi.org/10.1016/j.ijrobp.2011.03.029)
29. Strongin A, Yovino S, Taylor R, Wolf J, Cullen K, Zimrin A, et al. Primary tumor volume is an important predictor of clinical outcomes among patients with locally advanced squamous cell cancer of the head and neck treated with definitive chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2012; **82**: 1823–30. doi: [10.1016/j.ijrobp.2010.10.053](https://doi.org/10.1016/j.ijrobp.2010.10.053)
30. Hall WH, Ramachandran R, Narayan S, Jani AB, Vijayakumar S. An electronic application for rapidly calculating Charlson comorbidity score. *BMC Cancer* 2004; **4**: 94.
31. Kancherla KN, Oksuz DC, Prestwich RJ, Fosker C, Dyker KE, Coyle CC, et al. The role of split-course hypofractionated palliative radiotherapy in head and neck cancer. *Clin Oncol (R Coll Radiol)* 2011; **23**: 141–8. doi: [10.1016/j.clon.2010.09.006](https://doi.org/10.1016/j.clon.2010.09.006)
32. Agarwal JP, Nemade B, Murthy V, Ghosh-Laskar S, Budrukkar A, Gupta T, et al. Hypofractionated, palliative radiotherapy for advanced head and neck cancer. *Radiother Oncol* 2008; **89**: 51–6. doi: [10.1016/j.radonc.2008.06.007](https://doi.org/10.1016/j.radonc.2008.06.007)