Proton Radiotherapy for Recurrent or Metastatic Head and Neck Cancers with Palliative Quad Shot

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Abstract

Purpose: Some patients with previously treated, unresectable, recurrent or metastatic head and neck malignancies are not amenable to curative-intent treatment. Here, we investigated the quad-shot (RTOG 8502) regimen of hypofractionated proton radiotherapy (RT) in that patient population.

Materials and Methods: From 2013 to 2015, 26 patients with recurrent or metastatic cancers were treated with palliative proton RT to the head and neck with quad shot (3.7 Gy twice daily for 2 days). Patient characteristics and survival data were reviewed.

Results: Seventeen (65%) patients received ≥ 3 quad-shot cycles and 23 (88%) had prior head and neck RT. Overall palliative response was 73% (n = 19). The most common presenting symptom was pain (50%; n = 13), which improved in 85% (n = 22) of all patients. The overall grade-1 acute-toxicity rate was 58% (n = 15), and no acute grade 3 to 5 toxicities were observed.
Conclusions: The proton quad-shot regimen demonstrates favorable palliative response and toxicity profile, even in patients that received prior RT.

Keywords
proton therapy; palliation; head and neck cancers; quad shot; radiotherapy

Introduction
Appropriate management of previously treated, unresectable, recurrent or metastatic head and neck malignancies remain a clinical challenge [1]. Salvage, full-dose external beam radiation (EBRT) with or without systemic therapy may offer a meaningful survival benefit (10%–48% at 2 years) at the expense of increased risk and degree of toxicity [2, 3]. However, many patients are not amenable to curative-intent treatment because of tumor location, extent of disease, poor performance status, and comorbidities. Palliative radiotherapy (RT) is commonly used to control symptoms, improve quality of life (QOL), and possibly, prolong survival in these circumstances [2, 4, 5].

The optimal, palliative RT regimen has not been determined. In recent years, short-course hypofractionated RT has been considered more suitable than protracted, conventional-fractionation RT because it provides equivalent symptomatic improvement, tumor response, and survival outcomes while shortening overall treatment time and minimizing effects [5–7]. Although a variety of different hypofractionation schemes have been used clinically (from 2.5–8 Gy per fraction, to a total dose of 20–48 Gy), the quad shot regimen is believed to offer the best combination of efficacy, toxicity, and patient convenience [4, 8].

The RTOG 8502 regimen, colloquially referred to as quad shot, consists of 3.7 Gy twice daily for 2 consecutive days at 4-week intervals and was originally used for treatment of pelvic malignancies [9]. Early studies demonstrated overall tumor responses of 53% to 77%, with a 53% to 85% improvement in symptom palliation in patients with end-stage head and neck cancers [10–12]. We previously evaluated the combination of quad shot with intensity-modulated RT (IMRT) and demonstrated a comparable palliative response [5], with only 5% of patients experiencing grade 3 to 4 acute toxicities. This regimen is now our current institutional standard for patients requiring palliative RT for incurable cancers of the head and neck [5].

However, there remains a significant population of patients with advanced head and neck cancers who suffer from tumor-related symptoms but are no longer candidates for photon-based EBRT. Some tumors recur in a previously heavily irradiated region, limiting additional radiation because of the risk to adjacent healthy structures, such as the spinal cord, brain stem, and temporal lobe. Patients with locally invasive disease near radiosensitive organs at risk (OAR), including the optic nerve and optic chiasm, and patients unable to tolerate additional cycles of palliative RT after the first IMRT quad shot cycle because of treatment toxicities, are poor candidates for photon-based EBRT [5].

Proton therapy offers an alternative method of RT for patients for whom photon-based EBRT is suboptimal. Although IMRT is a highly conformal radiation technique, low to
intermediate doses to surrounding nontarget organs is unavoidable. In contrast to photon-based EBRT, proton therapy deposits most of the radiation energy within the target area rather than the surrounding healthy tissues outside the target volume. Proton therapy is preferable for patients with recurrent tumors in previously irradiated areas and tumors near radiation-sensitive structures because of its physical properties, which allow for a sharp drop-off in dose in the surrounding healthy tissues, including radiosensitive OARs (Figure).

To our knowledge, this is the first study evaluating the use of proton RT in palliation of head and neck cancers. We investigate palliative response, treatment toxicity, and survival of patients with incurable, recurrent or metastatic head and neck malignancies treated with palliative proton RT with quad shot.

Materials and Methods

Patients

This retrospective study was independently reviewed and approved by the institutional review board. In September 2013–15, 26 patients with incurable, recurrent or metastatic head and neck cancers were treated at our center with ≥1 cycle of palliative, hypofractionated proton RT to the head and neck with the quad shot regimen. Patients were determined ineligible for curative treatment by a multidisciplinary team generally because of the extent of their disease, medical comorbidities, and distant metastatic burden. Furthermore, 16 patients (62%) were considered poor candidates for further photon-based EBRT because of tumor location or previous local RT history.

Palliative Proton Radiotherapy

The palliative proton quad shot regimen prescribes 3.7 Gy relative biological effectiveness (RBE) per fraction, assuming an RBE value of 1.1. Each treatment cycle consisted of twice-daily fractions administered over 2 consecutive days to a total of 14.8 Gy (RBE) per cycle. Each cycle was repeated every 21 to 25 days in the absence of in-field disease progression or significant acute toxicity, as previously reported by Paris et al [10]. An additional rest period of 1 to 3 weeks between RT cycles was used in instances of acute toxicities or other concerns. Treatment volumes were reviewed before each cycle and replanned to account for tumor volume reduction for patients with significant response to therapy. The palliative radiation included both the symptomatic lesion, either primary site or regional disease, and any additional regional disease that could be safely treated.

Patients were treated with chemotherapy with cytotoxic or targeted agents at the discretion of the attending radiation oncologist and medical oncologist.

Radiotherapy Technique

Computed tomography (CT) imaging was used for patient simulation before each cycle with a thermoplastic 5-point head and neck mask. If available, positron emission tomography/CT or magnetic resonance imaging studies were fused to the CT simulation scan for target volume delineation. Gross tumor volume included symptomatic gross disease and other concerning large-volume disease and was identified through diagnostic imaging and clinical
examination, then contoured onto the CT simulation images by the radiation oncologist. A patient-specific clinical target volume (CTV) was added to cover adjacent areas at high risk for microscopic tumor spread at physician discretion. The planning target volume was created based on the CTV with an additional 3 to 5-mm margin dependent upon available imaging guidance during treatment and setup uncertainty. This was reduced to as low as 1 mm when near critical healthy tissues. In the distal beam direction, the plan was generated to cover the CTV, and the plan was evaluated for a range uncertainty of + 2.5% + 2 mm. A smear radius of 7 mm, equal to the lateral setup uncertainty, was used.

For patients with prior local RT, the spinal cord and brainstem were prioritized as the OAR, with 70 Gy as the maximum allowable limit. A constraint guideline of a total maximum point dose of 60 Gy in 2-Gy equivalents from all treatments was used. The RT was delivered with uniform scanning proton beams, with beam-specific apertures and compensators.

**Treatment Response and Toxicity Evaluation**

Palliative response was defined as subjective relief of presenting symptom(s) or objective reduction of the gross tumor, as determined though physical examination or radiographic tumor response. Evaluation of the objective tumor response was performed 4 to 12 weeks after the last cycle of RT. Positron emission tomography response criteria in solid tumors and Response Evaluation Criteria in Solid Tumor (version 1.1) were used. Toxicity was scored for all patients, with toxicity events according to the Common Terminology Criteria for Adverse Events (version 4.03), with acute toxicity defined as an adverse event occurring within 3 months of palliative RT completion.

**Statistical Methods and Definitions**

Follow-up was maintained until death or date of last contact. Overall survival (OS) was measured from start of palliative proton RT until the date of death or last follow-up. Progression-free survival (PFS) was calculated from the start date of palliative proton RT until the date of in-field tumor progression or death. The OS and PFS rates were determined by the Kaplan-Meier technique. A Spearman q test was used to examine correlation between palliative response and clinical factors.

**Results**

Twenty of the 26 patients (77%) were men, and the median age was 69 years (range, 35–89 years). The most common histology was squamous cell carcinoma (73%; n = 19), followed by adenocarcinoma (19%; n = 5) and nonanaplastic thyroid carcinoma (8%; n = 2). Recurrent T stage was as follows: rT0–2 (31%; n = 8) and rT3–4 (69%; n = 18). patients (35%) presented with distant metastasis before proton, palliative RT and the Karnofsky performance status (KPS) score was ≤ 70 in 18 patients (69%). All but 3 of the recurrent or metastatic lesions were located in nonlarynx sites. Fourteen patients (54%) Had surgical resection at the primary disease site, and 23 patients (88%) received prior RT to the palliative site, with a median dose of 70 Gy (25th-75th quartiles, 60–120 Gy). One patient (4%) underwent partial resection 2 months before palliative quad shot RT. Patient characteristics are summarized in Table 1.
Palliative Treatment.

Seventeen patients (65%) completed ≥3 cycles of quad shot (Table 2). Seven patients (27%) received treatment for the primary site of their disease, and the remainder (n = 19; 73%) received palliation for symptomatic, regional disease. Of the remaining 9 patients who did not receive ≥3 cycles of quad shot, 4 patients (44%) only received 1 RT cycle, one half because of local tumor growth, and the remaining half because of progression of distant metastatic lesions. The other 5 patients (56%) received only 2 cycles of proton palliative RT, 2 because of local tumor progression, 1 because of logistical concerns, and 2 converted to systemic palliation or supportive care because of concurrent distant metastases. Two of the 26 patients (8%) were previously treated with 1–2 quad shot cycles by IMRT.

Chemotherapy administration was at the discretion of the treating medical oncologist and was based on factors that included performance status and presence of systemic disease. Twelve patients (46%) received systemic chemotherapy as part of their palliative regimen. Chemotherapy was administered concurrently in 5 of the 26 patients (19%) patients and induction-concurrent adjuvant was administered in 7 patients (27%). Seven of those 12 patients (58%) received a targeted agent (5 received cetuximab and 1 each received pembrolizumab and cabozantinib). The remaining 5 patients received cytotoxic chemotherapy, with 2 receiving methotrexate and 3 with a combination of carboplatin and paclitaxel.

Presenting Symptoms and Response Analysis.

The most common presenting symptoms were pain (50%; n = 13), trismus (27%; n = 7), dysphagia (23%; n = 6), and visual deficits (19%; n = 5). Overall, 73% of patients (n = 19) had a palliative response at the completion of therapy. After completion of the first and second quad shot cycles, the palliative response rates were 35% (n = 9) and 68% (n = 15), respectively. Of the 17 patients (65%) who received 3 or more cycles of the quad shot regimen, 88% (n = 15) achieved a palliative response. Palliative response by presenting symptoms ranged from 19% for vision changes (n = 5 patients) to 100% for hemorrhage (2 patients). Pain was improved in 85% (n 22) of all patients (Table 2). Four patients (15%) achieved a complete response, 11 patients (42%) had a partial response, 5 (19%) had stable disease, and 6 (23%) developed disease progression.

Using Spearman’s rho rank correlation coefficient, palliative response was significantly correlated with increasing number of Quad Shot cycles (0.720; P < 0.001) but not with KPS, prior RT, prior surgery, palliative chemotherapy, histology or T/N stage (Table 3).

Survival Outcomes.

Median OS was 9.0 months (95% confidence interval [CI], 6.8–11.1) and median follow-up was 8.9 months. Nine patients (34.6%) had in-field tumor progression. Eight patients (30.8%) died, 1 from comorbidities, 3 from local tumor progression, and 4 from distant metastatic disease. Median PFS was 8.1 months (95% CI, 4.78–8.40).

On univariate analysis, age and a greater number of Quad Shot cycles were significantly associated with both PFS and OS (Table 4).
Toxicity.

No grade 3 to 5 acute toxicities were observed in our study. Grade 2 acute toxicities occurred in 2 patients (8%); 1 patient with recurrent soft-palate disease experienced mucositis, and 1 patient with recurrent cutaneous cancer had dermatitis. The rate of overall grade 1 acute toxicity was 58% (n = 15), with the most common adverse events being fatigue (8 patients; 31%) and dermatitis (6 patients; 23%). See Table 2 for a summary of the most common acute toxicities observed. Grade 3 late fibrosis was observed in 1 patient 5 months after their third quad shot cycle. The patient had a recurrent squamous cell carcinoma of the lip, which was heavily pretreated with 2 courses of radical photon-based EBRT.

Discussion

Incurable head and neck cancer has an extremely poor prognosis and is often accompanied by a heavy symptomatic burden because of constriction of the trachea and esophagus. The estimated median survival is 7–10 months even after active palliative treatment [1]. The median OS in our study was 9.1 months; however, our study demonstrated improved symptom response with the proton quad shot regimen. Although palliative systemic therapy can achieve acceptable tumor response rates ranging from 12% to 48% with less late toxicity [13], palliative RT remains an important option for patients with recurrent head and neck cancers who have local tumor progression or bulky tumor mass despite multiple lines of systemic therapy. Furthermore, proton palliative RT can benefit those who cannot receive photon-based palliative RT because of tumor location or prior local radiation, and it provides benefit to patients who have had previous radiation through decreased cumulative dose to sensitive surrounding tissue [14]. The proton quad shot regimen offers an alternative option for symptom palliation for patients not amenable to palliative photon RT.

To our knowledge, this is the first study reporting on proton therapy for palliation of head and neck malignancies. Treatment with the proton quad shot RT regimen in the current study achieved a palliative response rate of 73% (n = 19 patients); among whom, 63% (n = 12) were considered ineligible for additional photon-based RT. The overall tumor response rate (complete response + partial response) was 61% (n = 16 patients), which is comparable to other studies with palliative, short-course, hypofractionated palliative RT to treat recurrent head and neck cancers [4, 5, 8]. However, the toxicity rate among our cohort was quite low. Nonspecific grade 1 fatigue was the most commonly observed acute toxicity found in 31% of patients (n = 8), followed by grade 1 dermatitis in 23% of patients (n = 6). Grade 2 acute toxicities were observed in 2 patients (8%). The case of grade 2 mucositis was expected for the patient with a soft-palate recurrent tumor, and grade 2 dermatitis was observed in another patient with cutaneous disease.

The lower rates of toxicity observed may be due to a variety of factors. First, proton therapy offers the unique advantage of delivering a negligible radiation dose to healthy tissues behind the target volume. In our previous report on the palliative quad shot regimen study with IMRT to treat similar patients [5], the incidence of grade 2 to 3 acute toxicity was 33%, as compared with 8% (n = 2 patients) of grade 2 acute toxicity and an absence of grade 3 acute toxicities observed in the current study. It is not surprising that grade 1 dermatitis was
one of the most commonly observed toxicities considering the entrance of the high-energy proton beam through the skin. Even so, the skin dosage could be further minimized through pencil beam scanning with intensity modulation, which may decrease both the acute and late skin and superficial tissue toxicities [15]. Secondly, the quad shot regimen provided a much longer interval (4 weeks) for normal tissue repair after each RT cycle, which may reduce acute and late toxicities. Other studies [16–19] of hypofractionated, palliative RT with a total dose of 30 to 50 Gy in 5 to 16 fractions for 2 to 5 weeks demonstrated a decent palliative response but with grade 3 acute mucositis rates as high as 18% to 66%. Another study examined the “IHFSQ regimen (HypoFractionnée 2 Séances Quotidiennes)” of 3 Gy twice a day for 2 fractions, twice a week every other week for weeks 1 to 7 with concurrent, platinum-based chemotherapy for advanced head and neck cancers [20]. The reported grade 3 acute toxicity was only 4%, which is comparable to the 5% observed in our previous photon-based quad shot study with IMRT [5], whereas the median PFS was only 3.8 months [20]. Although acute toxicity evaluation was not standardized in this study, we believe the adverse events observed are representative of patients’ palliative symptom relief.

Three patients (12%) presented with late grade 3 to 4 toxicity, which is higher than expected for the enrolled irradiation-naïve patients. In comparison, no severe late toxicities were noted in numerous other studies of the quad shot regimen conducted at different institutions, independent of 2-dimensional RT or IMRT use [5, 10, 11, 17]. One patient in the prior studies with recurrent squamous cell carcinoma of the lip had late grade 3 fibrosis, likely from the cumulative effect of 2 courses of RT.

The quad shot regimen is currently the only hypofractionated RT method that allows target revision for each cycle of palliative RT to account for tumor shrinkage. The adaptive nature of this regimen allows for decreased healthy tissue dose [16–19]. Further RT is generally not offered for patients who did not benefit from previous cycles of the quad shot regimen because of tumor progression or other considerations, to avoid unnecessary side effects or ineffectual treatment. Therefore, the use of the proton quad shot regimen provides an alternative for patients not amenable to photon-based EBRT.

Although the proton quad shot regimen is beneficial for palliation, the expense of proton therapy cannot be overlooked. Although significantly more than photon-based RT, the cost of proton therapy is likely to decrease as the number of operational proton centers increases. Notwithstanding cost, the proton quad shot regimen balances effective palliation with toxicity, particularly in patients with previous courses of RT or lesions near critical structures. Additional work is needed to better delineate the value of proton therapy in this setting.

Our study reports on our institutional experience with incurable, recurrent or metastatic head and neck cancers. It is limited by its retrospective nature and the lack of a formal QOL assessment or standardized reporting of adverse events, including limitations of capturing of toxicity between cycles. However, the improvement in QOL can be inferred from the high rates of palliative and tumor response, as well as the notably low incidence and severity of toxicities. In conclusion, for patients with heavily treated, incurable, recurrent or metastatic head and neck cancer, proton hypofractionated palliative RT with the quad shot regimen
resulted in a 73% rate (19 of 26 patients) of palliative response with minimal acute and late toxicities. The quad shot regimen by proton therapy is safe and effective and serves as a feasible alternative for patients not amenable to photon-based RT. Prospective studies will be needed to address which patient population and clinical situations would benefit most from proton hypofractionated RT.

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References

1. Ho AS, Kraus DH, Ganly I, Lee NY, Shah JP, Morris LG. Decision making in the management of recurrent head and neck cancer. Head Neck. 2014;36:144–51. [PubMed: 23471843]
2. Strojan P, Corry J, Eisbruch A, Vermorken JB, Mendenhall WM, Lee AW, Haigentz M, Jr, Beiter JI, de Bree R, Takes RP, Paleri V, Kelly CG, Genden EM, Bradford CR, Harrison LB, Rinaldo A, Ferrito A. Recurrent and second primary squamous cell carcinoma of the head and neck: when and how to reirradiate. Head Neck. 2015;37:134–50. [PubMed: 24481720]
3. Duprez F, Berwouts D, Madani I, Bonte K, Boterberg T, De Gersem W, Deron P, Huvonen W, De Neve W. High-dose reirradiation with intensity-modulated radiotherapy for recurrent head-and-neck cancer: disease control, survival and toxicity. Radiother Oncol. 2014;111:388–92. [PubMed: 24998706]
4. Nguyen NT, Doerwald-Munoz L, Zhang H, Kim DH, Sagar S, Wright JR, Hodson DI. 0-7-21 Hypofractionated palliative radiotherapy: an effective treatment for advanced head and neck cancers. Br J Radiol. 2015;88:20140646. [PubMed: 25694259]
5. Lok BH, Jiang G, Guitontov S, Lanning RM, Sridhara S, Sherman EJ, Tsai CJ, McBride SM, Riaz N, Lee NY. Palliative head and neck radiotherapy with the RTOG 8502 regimen for incurable primary or metastatic cancers. Oral Oncol. 2015;51:957–62. [PubMed: 26282714]
6. Kalogeridi MA, Kouloulias V, Zygogianni A, Kyrgias G. Short-course hypofractionated radiochemotherapy for unresectable locally advanced cancer of the base of tongue: palliation only? a case report and short review of the literature. Radiation Oncol J. 2014;32(2):99–102.
7. Kanetchra KN, Okusz DC, Prestwich RJ, Fosker C, Dyker KE, Coyle CC, Sen M. The role of split-course hypofractionated palliative radiotherapy in head and neck cancer. Clin Oncol (R Coll Radiol). 2011;23:141–8. [PubMed: 20934860]
8. Johnstone C, Lutz ST. The role of hypofractionated radiation in the management of non-osseous metastatic or uncontrolled local cancer. Ann Palliat Med. 2014;3:291–303. [PubMed: 25841909]
9. Sرانos W, Jr, Guse C, Perez C, Grigsby P, Doggett RL, Poulter C. Phase II study of multiple daily fractionations in the palliation of advanced pelvic malignancies: preliminary report of RTOG 8502. Int J Radiat Oncol Biol Phys. 1989;17:659–61. [PubMed: 24764264]
10. Paris KJ, Sranos WJ, Jr, Lindberg RD, Jose B, Albrink F. Phase I-II study of multiple daily fractions for palliation of advanced head and neck malignancies. Int J Radiat Oncol Biol Phys. 1993;25:657–60. [PubMed: 7681051]
11. Corry J, Peters LJ, Costa ID, Milner AD, Fawns H, Rischin D, Poreeedu S. The ‘QUAD SHOT’—a phase II study of palliative radiotherapy for incurable head and neck cancer. Radiother Oncol. 2005;77:137–42. [PubMed: 16266054]
12. 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(12):1586–591. [PubMed: 18798313]
13. Pancari P, Mehra R. Systemic therapy for squamous cell carcinoma of the head and neck. Surg Oncol Clin N Am. 2015;24:437–54. [PubMed: 25979393]
14. Plastaras JP, Berman AT, Freedman GM. Special cases for proton beam radiotherapy: re-irradiation, lymphoma, and breast cancer. Semin Oncol. 2014;41:807–19. [PubMed: 25499639]
15. Depauw N, Batin E, Daartz J, Rosenfeld A, Adams J, Kooy H, MacDonald S, Lu HM. A novel approach to postmastectomy radiation therapy using scanned proton beams [published correction appears in Int J Radiat Oncol Biol Phys. 2016;95: 1086]. Int J Radiat Oncol Biol Phys 2015;91:427–34. [PubMed: 25636765]

16. Porceddu SV, Rosser B, Burmeister BH, Jones M, Hickey B, Baumann K, Gogna K, Pullar A, Poulsen M, Holt T. Hypofractionated radiotherapy for the palliation of advanced head and neck cancer in patients unsuitable for curative treatment—‘‘hypo trial.’’ Radiother Oncol. 2007;85:456–62. [PubMed: 18036889]

17. Agarwal JP, Nemade B, Murthy V, Ghosh-Laskar S, Budrukkar A, Gupta T, D’Cruz A, Pai P, Chaturvedi P, Dinshaw K. Hypofractionated, palliative radiotherapy for advanced head and neck cancer. Radiother Oncol. 2008;89:51–6. [PubMed: 18649633]

18. 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. [PubMed: 19373698]

19. Das S, Thomas S, Pal SK, Isiah R, John S. Hypofractionated palliative radiotherapy in locally advanced inoperable head and neck cancer: CMC Vellore Experience. Indian J Palliat Care. 2013;19(2):93–8. [PubMed: 24049349]

20. Monnier L, Touboul E, Durdux C, Lang P, St Guily JL, Huguet F. Hypofractionated palliative radiotherapy for advanced head and neck cancer: the IHF2SQ regimen. Head Neck. 2013;35(12):1683–8. [PubMed: 23359352]
Figure.
Quad shot proton treatment plan demonstrating optic nerve and cord sparing because of the sharp dose falloff of protons in a patient with verrucous carcinoma of the right alveolar ridge, with local recurrence in the right maxilla.
Table 1.

Baseline clinical and treatment characteristics.

| Baseline clinical and treatment characteristics (n = 26) | Results, No. (%) |
|--------------------------------------------------------|------------------|
| Age, y, median (range)                                  | 69 (35–89)       |
| Gender                                                 |                  |
| Men                                                    | 20 (77)          |
| Women                                                  | 6 (23)           |
| KPS                                                    |                  |
| ≤ 70                                                   | 18 (69)          |
| > 70                                                   | 8 (31)           |
| Histology                                              |                  |
| Squamous cell carcinoma                                | 19 (73)          |
| Adenocarcinoma                                         | 5 (19)           |
| Thyroid                                                | 2 (8)            |
| T stage<sup>a</sup>                                    |                  |
| T0–2                                                   | 7 (27)           |
| T3–4                                                   | 17 (65)          |
| TX                                                     | 2 (8)            |
| N stage<sup>b</sup>                                    |                  |
| N0                                                     | 9 (35)           |
| N1                                                     | 6 (23)           |
| N2                                                     | 8 (31)           |
| N3                                                     | 2 (8)            |
| NX                                                     | 1 (4)            |
| M stage                                                |                  |
| M0                                                     | 17 (65)          |
| M1                                                     | 9 (35)           |
| Recurrent stage                                        |                  |
| rStage II                                              | 1 (4)            |
| rStage III-IV                                          | 25 (96)          |
| Prior chemotherapy                                     |                  |
| Yes                                                    | 23 (88)          |
| No                                                     | 3 (12)           |
| Prior RT to quad shot site                             |                  |
| Yes                                                    | 23 (88)          |
| No                                                     | 3 (12)           |
| Median dose, Gy, No. (range)                           | 70 (48–320)      |
| Prior surgery for primary disease                      |                  |
| Yes                                                    | 14 (54)          |
| No                                                     | 12 (46)          |
| Salvage surgery before quad shot                        |                  |
| Yes                                                    | 1 (4)            |
| Baseline clinical and treatment characteristics (n = 26) | Results, No. (%) |
|--------------------------------------------------------|------------------|
| No                                                     | 25 (96)          |
| Cycles of quad shot                                     |                  |
| 1 (14.8 Gy)                                             | 4 (15)           |
| 2 (29.6 Gy)                                             | 5 (19)           |
| 3 (44.4 Gy)                                             | 10 (38)          |
| 4 (59.2 Gy)                                             | 7 (27)           |
| Palliative chemotherapy                                  |                  |
| Yes                                                     | 12 (46)          |
| No                                                      | 14 (54)          |
| Objective tumor response                                |                  |
| Stable disease                                          | 5 (19)           |
| Partial response                                        | 11 (42)          |
| Complete response                                       | 4 (15)           |
| Progression of disease                                  | 6 (23)           |

Abbreviations: KPS, Karnofsky performance status; RT, radiotherapy.

\( ^a \) Primary or recurrent T stage.

\( ^b \) Primary or recurrent N stage.
Table 2.
Presenting symptoms and palliative response by number of completed quad shot cycles and acute toxicities.

| Symptoms                          | Patients, No. (%) | Palliative response, No.\(^a\) (%) |
|-----------------------------------|-------------------|-----------------------------------|
| Presenting symptoms and palliative response |                   |                                   |
| Pain                              | 13 (50)           | 11 (85)                           |
| Dysphagia                         | 6 (23)            | 2 (33)                            |
| Hemorrhage                        | 2 (8)             | 2 (33)                            |
| Visual blurriness/deficits        | 5 (19)            | 1 (20)                            |
| Trismus                           | 7 (27)            | 5 (71)                            |
| Epistaxis                         | 2 (8)             | 1 (50)                            |
| Palliation achieved by histology  |                   |                                   |
| Squamous cell carcinoma           | 19 (73)           | 13 (68)                           |
| Adenocarcinoma                    | 5 (19)            | 4 (80)                            |
| Thyroid                           | 2 (8)             | 2 (100)                           |
| Time point when palliation achieved, cycles of quad shot completed |                   |                                   |
| 1                                 | 26 (100)          | 9 (35)                            |
| 2                                 | 22 (85)           | 15 (68)                           |
| 3                                 | 17 (65)           | 15 (88)                           |
| 4                                 | 7 (27)            | 7 (100)                           |
| Overall palliation achieved       |                   |                                   |
| Yes                               | 19 (73)           |                                   |
| No (symptoms persisted, worsened) | 7 (27)            |                                   |
| Acute toxicities observed in patients after quad shot (CTCAE) | Grade 1, No. (%) | Grade 2, No. (%) |
| Mucositis                         | 1 (4)             | 1 (4)                             |
| Trismus                           | 2 (8)             | 0 (0)                             |
| Fatigue                           | 8 (31)            | 0 (0)                             |
| Xerostomia                        | 2 (8)             | 0 (0)                             |
| Dermatitis                        | 6 (23)            | 1 (4)                             |

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events (version 4.03).

\(^a\)No. of responders based on time of best response.
### Table 3.
Spearman $\rho$ correlation of palliative response with patient and clinical factors.

| Characteristic | Palliation response (0 = no, 1 = yes) | Correlation coefficient | Sig. (2-tailed)$^d$ |
|----------------|--------------------------------------|-------------------------|---------------------|
| Age at palliative RT, y |                                      | 0.174                   | 0.394               |
| KPS on palliative RT visit |                                      |                         |                     |
| ≤ 70            |                                      | 0.058                   | 0.779               |
| > 70            |                                      |                         |                     |
| Histology       |                                      |                         |                     |
| Squamous cell carcinoma |                                  | −0.200                   | 0.327               |
| Adenocarcinoma  |                                      |                         |                     |
| Thyroid         |                                      |                         |                     |
| T stage$^b$     |                                      |                         |                     |
| T0–2            |                                      | −0.370                   | 0.075               |
| T3–4            |                                      |                         |                     |
| N stage$^c$     |                                      |                         |                     |
| N0–1            |                                      | 0.075                   | 0.429               |
| N2–3            |                                      |                         |                     |
| Prior RT to treated site |                                 | −0.259                   | 0.202               |
| Yes             |                                      |                         |                     |
| Surgery to primary site |                                | −0.040                   | 0.856               |
| Yes             |                                      |                         |                     |
| Palliative chemotherapy |                                | 0.214                   | 0.294               |
| Yes             |                                      |                         |                     |
| Cycles of quad shot |                                |                         |                     |
| 1               |                                      | 0.720                   | < 0.001             |
| 2               |                                      |                         |                     |
| 3               |                                      |                         |                     |
| 4               |                                      |                         |                     |

Abbreviations: RT, radiotherapy; KPS, Karnofsky performance status.

$^d$Bold results were considered significant.

$^b$Primary or recurrent T stage.

$^c$Primary or recurrent N stage.
Table 4.

Univariate analysis of local progression-free survival overall survival.

| Characteristic                      | OS   |         |         | PFS  |         |         |
|-------------------------------------|------|---------|---------|------|---------|---------|
|                                     | P value | HR | 95.0% CI | P value | HR | 95.0% CI |
| KPS                                 |       |      |         |       |      |         |
| ≤70*                                | 0.205 | 0.404 | 0.099   | 1.643 | 0.644 | 0.721   |
| > 70                                | 0.276 | 2.219 | 0.528   | 9.318 | 0.823 | 0.836   |
| Gender                              |       |      |         |       |      |         |
| Male*                               | 0.276 | 2.219 | 0.528   | 9.318 | 0.823 | 0.836   |
| Female                              |       |      |         |       |      |         |
| Age at quad shot start (continuous variable) | 0.281 | 0.962 | 0.896   | 1.032 | 0.016 | 0.935   |
| Histology                           |       |      |         |       |      |         |
| Squamous cell carcinoma*            | 0.415 | 0.576 | 0.153   | 2.169 | 0.316 | 0.506   |
| Adenocarcinoma                      |       |      |         |       |      |         |
| Thyroid                             |       |      |         |       |      |         |
| T stage                             |       |      |         |       |      |         |
| T0–2*                               | 0.436 | 1.908 | 0.376   | 9.685 | 0.208 | 0.472   |
| T3–4                                |       |      |         |       |      |         |
| N stage                             |       |      |         |       |      |         |
| N0–1*                               | 0.768 | 1.376 | 0.165   | 11.481| 0.690 | 1.533   |
| N2–3                                |       |      |         |       |      |         |
| M stage                             |       |      |         |       |      |         |
| M0*                                 | 0.967 | 1.031 | 0.243   | 4.369 | 0.589 | 1.438   |
| M1                                  |       |      |         |       |      |         |
| Prior radiotherapy to quad shot site|       |      |         |       |      |         |
| No*                                 | 0.271 | 0.444 | 0.105   | 1.883 | 0.615 | 1.705   |
| Yes                                 |       |      |         |       |      |         |
| Surgery at initial presentation     |       |      |         |       |      |         |
| No*                                 | 0.384 | 1.936 | 0.437   | 8.584 | 0.274 | 2.184   |
| Yes                                 |       |      |         |       |      |         |
| Palliative chemotherapy             |       |      |         |       |      |         |
| No*                                 | 0.466 | 0.586 | 0.139   | 2.465 | 0.849 | 0.880   |
| Yes                                 |       |      |         |       |      |         |
| Cycles of quad shot                 |       |      |         |       |      |         |
| 1*                                  | **0.003** | 0.260 | 0.107   | 0.633 | **0.001** | 0.167   |
| 2                                   |       |      |         |       |      |         |
| 3                                   |       |      |         |       |      |         |
| 4                                   |       |      |         |       |      |         |

Abbreviations: OS, overall survival; PFS, progression-free survival; HR, hazard ratio, 95% CI, 95% confidence interval; KPS, Karnofsky performance status.

*Bold results were considered significant.
\textsuperscript{b} Asterisks (*) show the reference group used for univariate analysis.

\textsuperscript{c} Primary or recurrent T stage.

\textsuperscript{d} Primary or recurrent N stage.