Cyclical hypofractionated radiotherapy technique for palliative treatment of locally advanced head and neck cancer: institutional experience and review of palliative regimens

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Background Effective palliation in patients with locally advanced head and neck cancer is important. Cyclical hypofractionated radiotherapy (Quad Shot) is a short-course palliative regimen with good patient compliance, low rates of acute toxicity, and delayed late fibrosis.
Objective To review use of the Quad Shot technique at our institution in order to quantify the palliative response in locally advanced head and neck cancer.
Methods The medical records of 70 patients with head and neck squamous cell carcinoma who had been treated with the Quad Shot technique were analyzed retrospectively (36 had been treated with intensity-modulated radiation therapy and 34 with 3-D conformal radiotherapy). They had received cyclical hypofractionated radiotherapy administrated as 14.8 Gy in 4 fractions over 2 days, twice daily, repeated every 3 weeks for a total of 3 cycles. The total prescribed dose was 44.4 Gy. Primary endpoints were improvement in pain using a verbal numeric pain rating scale (range 1-10, 10 being severe pain) and dysphagia using the Food Intake Level Scale, and the secondary endpoints included overall survival (OS), local regional recurrence-free survival (LRRFS), progression-free survival (PFS) and time to progression.
Results Pain response occurred in 61% of the patients. The mean pain scores decreased significantly from pre to post treatment (5.81 to 2.55, $P = .009$). The mean initial dysphagia score improved from 2.20 to 4.77 55 ($P = .045$). 26% of patients developed mucositis (≤ grade 2), with 9% developing grade 3-level mucositis. 12 patients had tumor recurrence. The estimated 1-year PFS was 20.7%. The median survival was 3.85 months with an estimated 1-year OS of 22.6%. Pain response (hazard ratio [HR], 2.69; 95% confidence index [CI], I .552-1.77) and completion of all 3 cycles (HR, 1.71; 95% CI, 1.003-2.907) were predictive for improved OS.
Limitations This study is a retrospective analysis.
Conclusion Quad Shot is an appropriate palliative regimen for locally advanced head and neck cancer.

Locally advanced head and neck squamous cell carcinoma (HNSCC) is often not amenable to curative therapy. The marked pain, bleeding, hoarseness, cough, and dysphagia that accompany this disease state often necessitate a palliative regimen of radiotherapy in lieu of a more aggressive approach to therapy. Palliative radiotherapy, in general, has the potential to greatly improve the quality of life (QoL) of these patients and may actually increase overall survival. The ideal palliative regimen would improve QoL, induce tumor response, and decrease inpatient admissions, all while concurrently minimizing the toxicity that results from radiotherapy.[1] Regimens for curative radiotherapy are more clearly delineated, but there is currently a paucity of literature on the ideal

Accepted for publication October 28, 2015. Correspondence: Neal E Dunlap, MD; nedunl01@louisville.edu. Disclosures: The authors have no conflicts of interests or financial disclosures. JCSO 2016;14:29-36. ©2016 Frontline Medical Communications. DOI 10.12788/jcso.0201.

fractionation schedule for palliation of locally advanced HNSCC.

Locally advanced HNSCC has historically been difficult to treat because of its large tumor size, the local invasion of critical structures, high hypoxic cell fraction centrally, and patient comorbidities that preclude a curative approach.[2] The traditional palliative dosing schedule for advanced HNSCC is 30 Gy/10 fractions over a 2-week period.[3] There is growing evidence, however, that a hypofractionated schedule may be more efficacious for several reasons, including increased patient compliance, better evaluation of treatment efficacy, lower rates of acute toxicity, and delayed late fibrosis. These concepts make the use of large fractions ideal in patients needing palliation, because it spares the early-responding tissues and ensures low toxicity for the duration of the patient's survival.

The cyclical hypofractionated regimen investigated here offers patients effective palliation, the benefits of which may be apparent clinically within days. This scheme, also known as the Quad Shot technique, was first piloted with good outcome in the 1970s by the MD Anderson Cancer Center and subsequently by the Radiation Therapy Oncology Group (RTOG) in the palliation of gynecologic malignancies. The regimen delivers 14.8 Gy in 4 fractions over a 2-day period, with fractions given twice daily with a minimum treatment interval of 6 hours. If no tumor progression is noted, this will be repeated every 3 weeks for a total of 3 cycles. The dosage schedule was designed to preserve a compact treatment schedule using an accelerated fractionation scheme, based on radiobiologic principles to achieve optimum tumor control while minimizing local, acute toxicity.[4,5] Similarly, regimens were adapted in Australia for palliation of head and neck cancer, using a slightly lower dose with good results.[6] Although multiple compact regimens have been described for palliation of head and neck malignancies, the original MD Anderson and RTOG technique has been refined and successfully adapted with comparable palliation and minimal toxicity.[1,4] Here, we review the efficacy of the Quad Shot technique as a palliative regimen using our institutional experience.

Methods

Patients

During June 2005 and November 2008, the medical records of 70 patients with HNSCC who had been treated with the Quad Shot technique were retrospectively reviewed at our institution (Brown Cancer Center, Louisville, KY). Eligible patients included those with advanced disease as defined the by AJCC [American Joint Committee on Cancer] Staging Manual (stages III and IV; 7th edition, 2010) who were not candidates for definitive therapy owing to disease extent, poor Karnofsky Performance Status (KPS) score, or refusal of conventional treatment. All of the patients had pathologic diagnosis of malignancy; 50 had primary tumors, and 20 had recurrent disease after initial surgical resection.

All of the patients were treated as part of a comprehensive, multidisciplinary head and neck cancer program that included palliative care by a board certified physician. They were started on opioid analgesics as part of the symptom management regimen and monitored by the palliative care team.

Treatment plan

The Quad Shot radiotherapy had been delivered as 14.8 Gy in 4 fractions, given twice a day, for 2 consecutive days with a minimal treatment interval of 6 hours. The regimen was repeated every 3 weeks for a total of 3 cycles provided there was no tumor progression or significant acute toxicity. The total planned prescribed was 44.4 Gy. Radiation therapy was delivered with photon energies in the 4-6 MV range. Patients were simulated with a customized mask (Aquaplast, Wycoff Heights, NJ) for immobilization, and the results of a planning computed-tomography (CT) scan was used to define target volumes. The radiotherapy volumes were reviewed before each radiotherapy cycle, and attempts were made to reduce the field size in the setting of tumor response. In all, 51% of patients (n = 36) were treated with intensity modulated radiation therapy (IMRT), with the remaining 34 treated with 3-dimensional conformal radiotherapy (3DCRT) techniques. The decision to use IMRT was determined by the treating physician but was primarily reserved for bulky disease approximating the spinal cord. Attempts were made to avoid the brainstem and spinal cord when possible. When 3DCRT techniques were used, off-cord field arrangements were used after the second treatment cycle to limit the spinal cord exposure to 30 Gy.

At our institution, we commonly administered low-dose paclitaxel (60 mg/m^2) on Day 1 of each radiation cycle for a total of 3 cycles. All of the patients were premedicated before every dose of paclitaxel to prevent hypersensitivity reactions. No patients were treated with adjuvant chemotherapy after completion of the planned 3 cycles of treatment.

Assessments and monitoring procedures

At the initial consultation, the patient's age, tumor location, tumor stage, KPS score, and weight were documented. Pretreatment symptoms of pain severity, dysphagia, voice quality, trismus, respiratory compromise, and neck edema were assessed. Pain was assessed using a verbal numeric pain rating scale (range 1-10, where 0 denoted no pain and 10, severe pain). Dysphagia was assessed using the Food Intake Level Scale (FILS),[7] ranging from 1 to 10 and where 1-3 denoted no oral intake; 4-6, oral intake and alternative nutrition; and 7-10, oral intake alone. Voice quality, trismus, respiratory compromise, and neck edema were assessed qualitatively by the treating physician.

Early treatment termination and overall elapsed treatment time were also documented and recorded. The decision to terminate treatment was made by the treating physician. Mostly commonly, treatment was discontinued for lack of tumor or pain response, declining performance status, and excessive toxicity. Acute radiation toxicity was evaluated by the clinician and graded on days 1 and 2 of each cycle of radiotherapy and at each subsequent follow-up, according to the Common Terminology Criteria for Adverse Events (version 3.0).[8] Late radiation toxicity was assessed and graded using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scale.[9] Tumor response was assessed by clinical assessment based on inspection and palpation as well as flexible nasolaryngoscopy and CT scan when indicated and was reported using the Response Evaluation Criteria in Solid tumors.[10]

Statistical analysis

All of the patients who received the first course of radiotherapy were accounted for in the analyses. The primary endpoints assessed were symptomatic improvement. Secondary endpoints included treatment toxicity, local recurrence-free survival (LRFS), progression-free survival (PFS), local control (LC), time to progression (TTP), and overall survival (OS). Survival endpoints were evaluated using the Kaplan-Meier method. LRFS and LC were defined as recurrence after therapy at the initial sites. TTP was defined as any recurrence, and PFS included any recurrence and death. OS was measured from the initiation of treatment until the date of death, as verified by a search of the Social Security Death Index. Cox regression analysis was used to correlate factors with symptomatic improvement using IBM SPSS Statistics software (Armonk, NY). Cox proportional hazard models were used to detect influence factors of LRFS, PFS, and OS.

Results

Patient and treatment characteristics

The median patient age was 66 years (range, 43-95 years), and the median KPS score was 70 (range, 40-90; Table 1). Primary sites included the oropharynx (n = 20), oral cavity (n = 19), larynx/hypopharynx (n = 17), neck disease with an unknown primary (n = 7), and major salivary gland (n = 7). In all, 50 patients had primary tumors, and 20 were recurrent after initial surgical resection. Fifteen patients had metastatic disease at the time of treatment. Of those with primary tumors (n = 50), most had T3/T4 primary tumors (n = 36) or advanced N3 nodal disease (n = 10).

All of the patients received short-acting opioid analgesics as part of their symptom management. Sixty percent of patients required long-acting opioids at the initiation of treatment. All 70 patients were scheduled to complete 3 treatment cycles for a total of 44.4Gy, but only 53 (76%) completed all of the cycles. The median radiation dose delivered was 44.4 Gy (range, 12.9-44.4). Thirty-nine patients (56%) received concurrent chemotherapy. Eighty-percent received the planned 3 cycles of paclitaxel. The median elapsed treatment time from the initiation of radiation to completion or discontinuation was 42 days (range, 2-70).

TABLE 1 Patient and treatment characteristics

Characteristic	Value
Median age, y (range)	66 (43-95)
Karnofsky Performance Status (median, range)	70 (40-90)
Primary tumor site, n (%)	
Oropharynx	20 (29)
Oral cavity	19 (27)
Larynx/hypopharynx	17 (24)
Neck (unknown primary)	7 (10)
Major salivary gland	7 (10)
Tumor presentation, n (%)	
Primary	50 (71)
Recurrence	20 (29)
Median radiation dose, Gy (range)	44.4 (12.9-44.4)
Chemotherapy, n (%)	39 (56)
Median elapse treatment time, d (range)	42 (2-70)

Treatment toxicity and symptom response

The median follow-up was 4 months (range, 1-30). Treatment was well tolerated in most patients (Table 2). The reported incidence of grade 2 or higher mucositis and dermatitis was 26% and 17%, respectively. No patients experienced grade 4 or 5 toxicity. Grade 3 toxicity was limited to 4 patients (9%) who experienced mucositis. No factors were found to correlate with increased toxicity, including the use of chemotherapy, completion of planned 3 cycles, or radiation technique (data not shown).

Treatment response was evaluated based on the reduction of presenting symptoms and evaluated at the patient's last follow-up (Table 2). All of the patients presented with pain. Pain response was evaluated using a patient self-reported verbal numeric pain scale (range 1-10, where 0 denoted no pain and 10, severe pain). Initial assessment was made after the start of opioid analgesics in the initiation of opioid medications to minimize opioid medication as a confounder. Partial response was defined as a reduction from the presenting score without complete resolution. Thirty-nine percent of patients had a complete pain

TABLE 2 Treatment-related toxicity and palliative response to treatment[a]

Treatment-related toxicity	Response, n (%)
Acute toxicity	
Mucositis (> grade 2)	18 (26)
Dermatitis (> grade 2)	12 (17)
Pain (n = 70)	
Complete response	27 (39)
Partial response	16 (22)
No change	27 (39)
Dysphagia (n = 46)	39 (85)
Trismus (n = 14)	4 (29)
Neck edema (n = 27)	16 (59)
Respiratory compromise (n = 8)	6 (75)
Hoarseness (n = 6)	4 (67)
Chemotherapy, n (%)	39 (56)
Median elapse treatment time, d (range)	42 (2-70)

[a]Treatment response was evaluated based on the reduction of presenting symptoms and evaluated at the patient's last follow-up.

response, and 22% had a partial response at last follow-up. The mean pain score significantly decreased at from initial evaluation to last follow-up (5.81 to 2.55, P = .009). No significant predictors for pain response were identified on univariate analysis when controlling for opioid use.

Dysphagia response was evaluated at last follow-up, at which point 85% patients presenting with dysphagia had improvement in the degree of symptoms (using the FILS, where 1-3 denoted no oral intake; 4-6, oral intake and alternative nutrition; and 7-10, oral intake alone). The mean initial dysphagia score was 2.20 (SD, 1.35) and the mean posttreatment score was 4.77 (SD, 2.43; P = .045). On univariate analysis, complete response to pain (likelihood ratio, 2.494, 95% confidence index [CI], 1.029-6.973) was the only significant predictor for improved swallowing on dysphagia scales.

Trismus, neck edema, respiratory compromise, and hoarseness were physician-reported outcomes. Improvements in trismus were minimal, where neck edema, respiratory symptoms and hoarseness were generally improved with treatment. The reduction in opioid analgesic use was not quantified.

Patient outcomes

The median survival from the completion of treatment for the cohort was 3.85 months (95% CI, 2.19-5.49). The estimated 6-month and 1-year survival was 40.1% and 22.6%, respectively. Eighty-three percent of patients who were alive at 1 year remained disease free (n = 15). A Cox proportional hazard model showed significant factors for predicting death (Table 3). No pain response with treatment (hazard ratio [HR], 2.69; 95% CI, .552-1.77) and failure to complete all 3 cycles of radiation (HR, 1.71; 95% CI, 1.003-2.907) were predictive for increased risk of death. The estimated 1-year OS for patients with complete pain response and partial response compared with no response was 40% and 18%, respectively (P = .011; Figure 1). The estimated

TABLE 3 Cox proportional hazard model for patient and treatment related factors predicting death

Factor	HR	95% CI	*P* value
Age	1.004	.984-1.024	.706
Tumor location	1.368	.460-4.069	.505
Primary vs recurrence	1.048	.596-1.842	.872
KPS	.992	.974-1.011	.399
Radiation dose	1.002	.999-1.028	.056
Chemotherapy	1.615	.948-2.751	.078
Local recurrence	.997	.505-1.966	.993
Pain response			
Response	.991	.552-1.776	.974
No response	2.693	1.366-5.309	.004
Early therapy termination	1.707	1.003-2.907	.049
Metastatic disease	.907	.498-1.654	.750

CI, confidence index; HR, hazard ratio; KPS, Karnofsky Performance Scale

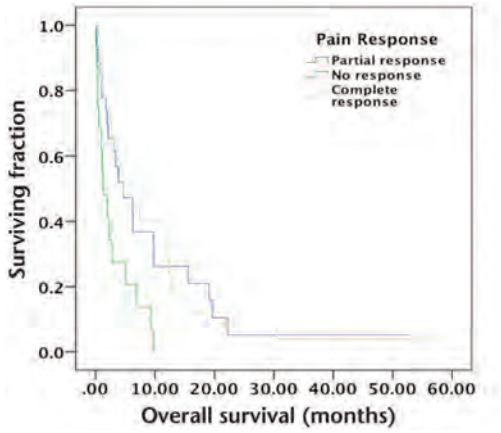

FIGURE 1 Overall cohort survival as a function of time from diagnosis to death of any cause, divided into groupings based on degree of pain response.

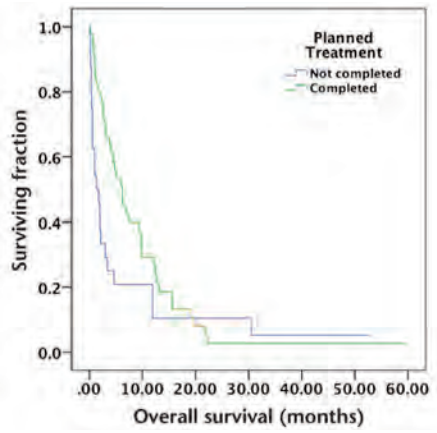

FIGURE 2 Overall cohort survival as a function of time from diagnosis to death of any cause, based on completion of planned cycles of treatment.

1-year OS for patients who completed all planned radiation and those who did not, was 30% and 20%, respectively (P = .046; Figure 2).

Of 12 patients who had tumor recurrence, 6 recurrences were local. The median LRFS was not reached. The estimated 6-month and 1-year local control rates were 95.6% and 73.8%, respectively. No patient or treatment related factors were predictive of improved local tumor control.

The median time to progression was not reached. The median PFS was 3.4 months (95% CI, 1.8-5.0). The estimated 6-month and 1-year PFS was 37.9% and 20.7%, respectively. No patient or treatment-related factors were predictive of improved local tumor control.

Discussion

Radiotherapy is the primary modality of treatment for patients with locally advanced, incurable HNSCC, so optimization of the fractionation schedule is foremost in ensuring that the goals of palliative therapy are met. A more hypofractionated regimen has been shown to be promising in meeting these ends by improving QoL, inducing tumor response, decreasing hospitalizations, and minimizing radiation toxicity.[1] Patients who present with locally advanced HNSCC often have severe pain, dysphagia, and compressive symptoms that necessitate relief through some form of targeted therapy. Currently, there is no clear guidance in the literature about an optimal palliative radiotherapy regimen. However, several hypofractionated regimens have been delineated (Table 4).

Many alternative palliative radiation schedules for locally advanced HNSCC are more protracted and require a greater number of fractions to achieve the goals of palliation. Many of these regimens produce good symptomatic relief at the cost of acute toxicity. For example, Agarwal and Al-Mamgani used 50 Gy/16 or 20 fractions and revealed good 1-year local control (55% and77%, respectively) and an OS of 3.3-17 months. However, significant grade 3 dermatitis (14% and 43%, respectively), mucositis (65% and 66%, respectively), and dysphagia (45%).[11,12] Porceddu and colleagues have reported on high rates of acute toxicity (11% dermatitis, 26% mucositis, 17% dysphagia).[13] The Quad Shot regimen boasts similar response rates and survival with dramatically reduced acute toxicity.

Chen and colleagues directly compared the Quad Shot schedule to 4 continuous-course, once-daily treatment regimens. Despite fairly low enrollment numbers, response was comparable among all regimens (83% for Quad Shot and 60%-86% for all other regimens), as was survival (4 months and 3-8 months). What differed markedly were the rates of grade 3 or higher toxicity (9% and 20%-42%). Of the 5 dosing schedules they investigated, the Quad Shot schedule was deemed to be the regimen of choice because of the lower toxicity.[4] That reiterates the fact that these various fractionation schedules are not radiobiologically equivalent. The consideration of local toxicity is paramount in the treatment of HNSCC, because the region lends itself to a unique side effect profile that can significantly impair a person's functional status.

Since the introduction of the Quad Shot regimen in the 1970s for the palliation of gynecologic malignancies, it has been refined and expanded for use as a treatment for head and neck malignancies. Paris and colleagues conducted research at our institution in the early 1990s to investigate the use of the Quad Shot regimen in the palliation of HNSCC. They recognized that a protracted course of radiotherapy in patients who needed palliation would not offer great benefit because of the duration of treatment as well as its acute toxicity. Their study assessed outcomes on the basis of patients' subjective responses, their decreased need for analgesics, and weight gain.

TABLE 4 Review of published palliative regimens for head and neck cancer

Study	n	Population	Dose	Time	Response, %
Agarwal[11]	110	Unresectable HNSCC	40 Gy/16 fx ± 10 Gy/4 fx	once daily	10 CR 63 PR
Al-Mamgani[12]	158	Unresectable HNSCC	50 Gy/16 fx	once daily	45 CR 28 PR
Biswal[3]	26	Stage IV HNSCC	30 Gy/10 fx ± 30 Gy/15 fx (split course)	once daily ± 4-wk break	54 CR 23 PR
Carracosa[1,a]	19	Pelvic or H&N tumors	44.4 Gy/12 fx + paclitaxel (Quad Shot)	BID x 2 d every 3 wks	26 CR 68 PR
Chen[4]	23*	Metastatic HNSCC	44.4 Gy/12 fx (Quad Shot)	BID x 2 d every 2-3 wks	83 OR
Corry[6]	30	Metastatic or incurable HNSCC	42 Gy/12 fx (Quad Shot)	BID x 2 d every 4 wks	7 CR 47 PR
Das[20]	36	Inoperable H&N cancer	40 Gy/10 fx	2 fx per wk	NR
Ghoshal[15]	15	Inoperable H&N cancer	28 Gy/8 fx (Quad Shot)	BID x 2 d every 3 wks	87 OR
Kancherla[17]	33	Locally advanced HNSCC (M0)	40 Gy/10 fx (split course)	once daily with built-in break	39 CR 33 PR
Monnier[21]	78	Metastatic or advanced HNSCC	48 Gy/16 fx + chemo	BID days 1, 3 on weeks 1, 3, 5, 7	5 CR 48 PR
Paris[14]	37	Incurable H&N tumors	44.4 Gy/12 fx (Quad Shot)	BID x 2 d every 3 wks	28 CR 49 PR
Porceddu[13]	35	Incurable HNSCC	30 Gy/5 fx ± 6 Gy/1 fx	2 fx per wk	43 CR 31 PR

bid, twice a day; CR, complete response; fx, fraction; G, grade; Gy, gray unit; H&N, head and neck; HNSCC, head and neck squamous cell carcinoma; LC, local control; MS, median overall survival; NR, not reported; OR, overall response; OS, overall survival; PFS, progression-free survival; PR, partial response; qid, 4 times a day; wk, week

[a]Subset of 60 patients.

Acute toxic effects, such as mucositis and dermatitis, were not quantified, nor was specific symptom control. No hazard models were used to illustrate particular metrics as prognosticators for OS.[14] Carrascosa and colleagues further refined the technique in 2007 by adding paclitaxel as a radiosensitizer before administration of each cycle. Their study enrolled patients with pelvic and head and neck malignancies and included just 7 cases of HNSCC.[1] Despite that, these studies established our institution as a pioneer in applying this technique in a palliative setting and revealed the potential benefits of Quad Shot when applied to HNSCC.

Pain reduction and swallowing improvements are significant endpoints to evaluate because they have a substantial impact on patient quality of life. It can be challenging to evaluate the benefits of the Quad Shot regimen in the multidisciplinary setting because there are many confounders, such as opioid analgesics. In our evaluation, we tried to minimize the impact of pain medications on symptomatic improvement to ascertain the stand-alone benefit of the Quad Shot. In addition, self-reported numeric pain scales are easy to administer but may oversimplify the evaluation of pain. More recent studies pertaining to the Quad Shot at other institutions, reported improvement in the presenting pain symptoms in 56%-90% of patients, with only 5%-9% of patients experiencing grade 3 or higher dermatitis or mucositis.[1,4,6,15] By comparison, our retrospective study of the Quad Shot method involved 70 patients, and

Toxicity		Local control or PFS	Survival
Early	**Late**		
14% G3 skin 66% G3/4 mucositis	54% G2 xerostomia 9% G3 xerostomia 13% G2 fibrosis	55.1% LC @ 1 y	3.3 mo MS
45% G3 skin 65% G3 mucositis 45% G3 dysphagia	43% ≥G2 @ 1 year 4.5% crude G4	77% LC @ 1 y 50% LC @ 2 y	17 mo MS
NR	NR	NR	76% @ 1 y 12 mo MS
1 G3 mucositis 2 G2 paclitaxel allergies	NR	Median symptom control 36 wks	4.5 mo MS
9% G3+ any toxicity	NR	NR	4 mo MS
0% ≥G2 mucositis 37% G2 xerostomia	27% ≥G1 xerostomia	Median LC 5.7 mo if CR/PR	5.7 mo MS
18% G3 mucositis 3% G3 dermatitis 23% G3 pain	NR	NR	7 mo MS
13% G2 mucositis 0% ≥G3 mucositis 0% ≥G2 dermatitis	NR	Mean PFS 3 mo	NR
3% G3 dermatitis 6% G3 mucositis 9% G3 esophagitis	NR	35% PFS @1 y 25% PFS @ 2 y	9 mo MS 42% OS @ 1 y 35% OS @ 2 y
4% ≥G3 overall 53% G2 mucositis 17% G2 skin	19% ≥G3 overall 12% fibrosis 7% xerostomia	Median PFS 10.3 mo 1 y PFS 52%	12.9 mo MS 58% OS @ 1 y
Not quantified (minimal)	NR	NR	4.5 mo MS
26% G3 mucositis 17% ≥G3 dysphagia 11% G3 skin	10% mucosa 10% xerostomia 10% skin	Median PFS 3.9 mo	6.1 mo MS

56% and 62% showed some improvement in dysphagia and pain, respectively. Only 4 patients (6%) experienced grade 3 mucositis.

It has yet to be determined whether the Quad Shot regimen improves patient. Our series showed a median survival was 3.9 months, with 1-year PFS and LRFS at 68% and 85%, respectively. These survival statistics are favorable when compared with other hypofractionated regimens and with supportive care alone, which portends a 1-year survival rate of about 13%.[16] As noted, complete pain response and completion of all planned cycles of radiation were predictive for improved OS. The estimated 1-year OS for patients who experienced complete pain response compared with minimal or no response was 40% and 18%, respectively. Likewise, the estimated 1-year OS for patients who completed all planned cycles compared with those who did not, was 30% and 20%.

The Quad Shot dosing scheme affords several benefits to both patients and clinicians. The decreased treatment duration and fewer fractions promote greater patient compliance and allows for fewer trips to the treatment center. The cyclic nature of the schedule also allows a larger dose of radiation to be given with each cycle, yet just below that which would produce mucosal inflammation and fibrosis.[6,12] Normal mucosal epithelial cells have a chance to regenerate between subsequent cycles, maintaining the integrity of the healthy tissues. The time between cycles also allows the practitioner to assess tumor response and

radiation-induced toxicity in the patient and administer repeated cycles only in patients showing good tumor response with acceptable toxicity.[6] Practitioners thus have the ability to limit futile treatment and defer the remaining treatments especially in patients with decline performance status despite palliation from pain. From a toxicity standpoint, the larger fraction size typically produces relatively greater damage to late responding tissues, that is, tissues that manifest radiation damage months to years after the radiotherapy has been completed.[17,18] Late effects, while significant in patients undergoing curative therapy, are less relevant for palliative patients with a shorter lifespan.

An important consideration is the selection of appropriate patients for a hypofractionated palliative regimen. Erkal and colleagues found nodal and symptomatic response rates to be similar after either continuous-course or hypofractionated radiotherapy, and they further acknowledged that the dose fractionation scheme should be tailored based on anticipated survival and patient characteristics.[19] KPS, age, disease burden at presentation, comorbidities, and previous attempts at surgical cure should be assessed because they are prognosticators that could influence the efficacy of palliation. Patients who are deemed to have longer lifespans based on such criteria may be found to suffer from late toxicity of radiotherapy and may therefore be less appropriate candidates for this regimen.

Despite the apparent advantages seen with using cyclical hypofractionation for effective palliation some limitations exist with our study. This data represents a retrospective analysis at a single institution. This regimen has been adapted from an original regimen applied to gynecologic malignancies and should be further tested in a prospective fashion to more adequately define the effect on pain relief, dysphagia improvement and toxicity.

Conclusions

As radiotherapy schedules are individualized for patients in need of palliation from locally advanced HNSCC, the Quad Shot regimen has been shown here to offer great benefit in terms of symptom relief and survival without the harm of local, acute toxicity. Physicians should consider integrating Quad Shot in comprehensive palliative management schemes in advanced HNSCC.

Acknowledgment

This paper was originally accepted for poster presentation at the annual meeting of the American Society of Radiation Oncology on September 15, 2014 in in San Francisco, California.

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