

Scientific Article

Rapid and Durable Symptom Palliation With Quad Shot Radiation Therapy to Nonosseous Metastatic/Recurrent Cancer in Elderly or Frail Patients in a Rural Community Clinic



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Abstract

More than half of patients with cancer receiving radiation therapy (RT) are treated in a palliative setting. Elderly or frail patients with metastatic/recurrent cancer require palliative RT that can provide a rapid cancer-related symptom response with low toxicity and short overall treatment time. Cyclical hypofractionated RT (quad shot: 14-14.8 Gy/4 fractions, twice-daily treatments with 6-hour intervals on 2 consecutive days monthly to a total of 42-44.4 Gy) can be a practical palliative RT regimen for patients with poor performance status. In this report, we present palliative symptom response and objective tumor response after quad shot for elderly or frail patients with nonosseous metastatic/recurrent cancers in various sites with varying histology.

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Introduction

Palliative radiation therapy (RT) is a well-established treatment to help patients manage the symptoms of advanced and metastatic cancer.¹ RT courses of 8 to 40 Gy given in 1 to 20 fractions once daily are widely accepted in the palliative setting. Effectiveness of these various palliative RT regimens has been evaluated extensively in patients with pain from osseous metastases.² A single fraction of 8 Gy has shown to be as effective as

longer protracted RT regimens for painful uncomplicated osseous metastases.³

Unlike osseous metastases, symptoms from nonosseous metastatic/recurrent cancers can vary from local pain to uncontrolled bleeding or infection, mechanical obstruction, or pressure at affected sites. Empirically, the same palliative RT regimens have been used for both osseous and nonosseous metastatic/recurrent sites; however, effectiveness of palliative RT for various symptoms from nonosseous metastatic/recurrent cancer has not been rigorously compared among different RT regimens as was done for painful osseous metastases. Thus, selection of palliative RT regimen for nonosseous metastatic/recurrent sites has been dependent on patient's general condition and availability of other palliative care. In clinic, short-course yet effective palliative RT regimens are preferred over protracted RT regimens for patients with poor performance status or

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significant comorbid disease. Although 8 Gy in 1 fraction would be appropriate for uncomplicated bone metastasis palliation, the tolerance for this dose has not been reported in elderly or frail patients with non-osteous metastatic/recurrent cancer.

A cyclical hypofractionated RT known as quad shot, which was formulated originally for advanced pelvic malignancies, has been implemented successfully for palliative treatment of head and neck cancers.⁴⁻⁷ Quad shot regimen consists of 14 to 14.8 Gy in 4 fractions over 2 consecutive days with the opportunity to repeat this same dosing for a total of 3 times at 4-week intervals, for a potential total dose of 42 to 44.4 Gy. Symptom response rate of 55% to 67% after the first quad shot (QS1) and over 80% after the third quad shot (QS3) has been reported in head and neck cancer patients.⁵⁻⁷ Thus, quad shot can be an effective palliative RT regimen to achieve rapid symptom relief in frail older patients with nonosseous metastatic/recurrent cancer. Two consecutive days of treatment per each quad shot and the flexibility of administering subsequent quad shots can also be practical and convenient for patients with poor general conditions. Radiobiologic effectiveness of 3 or more cycles of quad shot is reportedly comparable to that of protracted definitive RT regimens, and hypofractionation may provide particular benefit to radio-resistant low alpha-beta ratio cancers.⁸⁻¹¹ Herein, we report responses from palliative RT using quad shot in elderly or frail

patients with nonosseous metastatic/recurrent cancer in various anatomic sites with varying histology.

Methods and Materials

Patients

From 2018 to 2021, a total of 12 elderly or frail patients with nonosseous metastatic/recurrent cancer were treated at a community radiation oncology clinic with palliative RT using quad shot. Median patient age was 77 years (range 49-95) with Karnofsky performance score of 40% to 70%. Patients had histologically confirmed metastatic/recurrent cancers from melanoma, papillary thyroid carcinoma, Ewing sarcoma, adenocarcinoma of lung, or urothelial carcinoma. Metastatic/recurrent sites included scalp, neck muscle, breast, chest wall, parotid gland, brachial plexus, bladder, cystectomy bed, pelvic/inguinal lymph nodes, and tumor thrombus in iliac vessels. One patient with Karnofsky performance score of 40 and dementia had a locally advanced adenocarcinoma of the rectum. Local symptoms from metastatic/recurrent cancer comprised intractable pain, uncontrolled bleeding, antibiotic-resistant cellulitis, or obstructive symptoms such as edema in extremities, urinary retention, or constipation (Table 1). All patients declined or were determined ineligible for

Table 1 Patient and disease characteristics

Cases	Age	Diagnosis	Sites	Symptoms	KPS	RT	Response
1	95 y	Recurrent urothelial carcinoma	Bladder	Hematuria	60	QS1	No hematuria after QS1 until death at 9 mo after
2	85 y	Metastatic papillary thyroid carcinoma	Chest wall	Pain	50	QS3	Less pain after QS1. No pain after QS3 until death at 5 mo after QS1
3	79 y	Recurrent urothelial carcinoma	Cystectomy bed	Pain, leg edema	50	QS3	Less pain and leg edema after QS1. No leg edema after QS3 until death at 4 mo after QS1
4	73 y	Metastatic Ewing sarcoma	Parotid gland	Macroscopic tumor resection	70	QS3	Alive without local recurrence at 14 mo after QS1
5	82 y	Metastatic adenocarcinoma of lung	Brachial plexus	Pain, unable to use affected arm	60	QS3	Less pain and improved arm mobility after QS1 and symptoms continuously improved after QS3. F/U loss after QS3
6	75 y	Metastatic melanoma	Neck muscle	Pain	60	QS2	Less pain after QS1. No pain after QS2 until death at 3 mo after QS1
7	75 y	Metastatic melanoma	Breast	Pain	50	QS1	Less pain after QS1 until death at 1.5 mo after QS1
8	92 y	Metastatic small cell carcinoma	Bladder	Hematuria, urinary retention	70	QS3	No hematuria and less urinary retention after QS1. No symptoms after QS3
9	92 y	Adenocarcinoma of rectum	Rectum	Constipation, hemochezia	40	QS3	Improved bowel movement with less hemochezia after QS1. Complete symptom relief after QS3
10	71 y	Metastatic urothelial carcinoma	Inguinal and iliac lymph nodes	Cellulitis at inguinal area, Pain, leg edema	60	QS3	Resolved cellulitis, less pain and leg edema after QS1. Further improved symptoms with QS3
11	64 y	Metastatic melanoma	Scalp	Rapidly regrew after surgery	70	QS3	Stable melanoma after QS1 and regressed after QS3
12	49 y	Tumor thrombus from adenocarcinoma of lung	Iliac vessels	Pain, Leg edema	40	QS1	Complete resolution of pain and leg edema after QS1 until death at 2 mo after QS1

Abbreviations: F/U = follow up; KPS = Karnofsky performance score; QS = quad shot; RT = radiation therapy.

surgery or systemic chemotherapy or immunotherapy as palliative care because of their age or frail condition. During radiation oncology consultation, patients and their families requested rapid symptom relief with limited trips to the radiation oncology clinic. Therefore, various palliative RT regimens including a single fraction (8-10 Gy) RT and quad shot were discussed with patients and their families. All 12 patients and their families elected to try QS1 first and decide on further RT thereafter.

Radiation therapy

Patients underwent computed tomography (CT)-simulation scans for planning quad shot RT. The gross tumor volume (GTV) included symptomatic metastatic/recurrent disease and was identified through diagnostic images and physical examination when appropriate. A clinical target volume was the same as a GTV. A 0.5 to 1.0 cm margin was added to GTV to create a planning target volume (PTV). 3.5 Gy per fraction (3.5 Gy/fx) given twice a day, 6 hours apart, for 2 consecutive days, was prescribed to cover PTV using 3-dimensional conformal RT or intensity modulated RT. Depending on the location of the tumor, a custom bolus was applied to ensure the tumor received the full prescription dose. Planning objectives required the PTV coverage of 95% to 110%. Radiation dose to the spinal cord, brain stem, and optic nerve/chiasm was limited to 9 Gy per quad shot. For other organs at risk, the constraints were as low as reasonably achievable and followed suggestions from published recommendations.⁸ For subsequent quad shots, patients underwent new CT-simulation scans to revise PTVs accounting for tumor response from previous quad shot.

Response from quad shot RT

Palliative response was defined as subjective relief of initial presenting symptoms through patient-reported

outcomes in clinic notes. In cases with multiple symptoms at 1 site, palliative response was evaluated for each symptom. Evaluation of the objective radiographic tumor response was performed by comparison of GTVs on CT-simulation scans for each quad shot and the latest diagnostic images such as CT, magnetic resonance imaging, or positron emission tomography-CT scan as available. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (RECIST Working Group) was used to determine objective response by attending radiation oncologist, defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease. Follow-up interval was defined as beginning of QS1 until date of last contact or death.

Statistics

Statistical analysis of GTV comparison on each quad shot was done using a Student *t* test. A probability level of $P < .05$ was considered significant.

Results

Of the 12 patients, 8 (66.7%) completed QS3. After achieving complete symptom resolution with QS1, 2 patients did not pursue additional quad shot. One patient developed rapid deterioration of general condition, albeit with local symptom relief after QS1. One patient died of disease progression at a nonirradiated area after the second quad shot (QS2).

All 12 patients reported notably decreased symptoms at 2 to 3 weeks after QS1 (overall subjective palliative response rate of 100%). Hematuria from recurrent urothelial carcinoma and metastatic small cell carcinoma (1 site each) and cellulitis from metastatic urothelial carcinoma (1 site) were completely resolved after QS1. [Figure 1](#) shows a patient who achieved complete symptom resolution (edema and pain in left leg) after QS1 to intractable

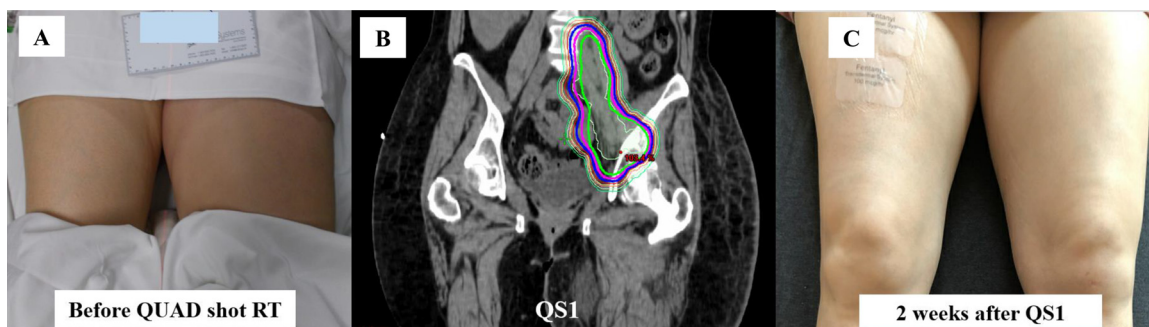


Fig. 1 A 49-year-old patient with multiple metastatic adenocarcinoma of lung presenting with edema and pain of left thigh from malignant thromboembolisms in the left iliac vessels (A). Coronal view of radiotherapy plan for first QUAD shot to the left iliac vessels (B). The patient achieved complete symptom resolution at 2 weeks after first quad shot (C). *Abbreviations:* QS = quad shot; RT = radiation therapy.

Table 2 Radiation targets comparison between CT-simulation scans for each quad shot (n = 8)

	QS1	QS2	QS3
GTV (mean), cm ³	359.3	172.6	117.4
GTV changes			
QS1 vs QS2	−42.7% (range 15.2%-83.6%), <i>P</i> = .02		
QS1 vs QS3	−67.4% (range 49.4%-86.7%), <i>P</i> = .01		
<i>Abbreviations:</i> CT = computed tomogram; GTV = gross tumor volume; QS = quad shot.			

malignant thromboembolisms in the left iliac vessels. Patients who received subsequent quad shots reported further relief of residual symptoms from QS2 and QS3 (Table 1).

Of the 8 patients who received QS3, tumor response was evaluated by comparing GTVs on CT-simulation scans for each Quad shot. Comparing GTVs (mean) at QS1 (359.3 cc), there was 42.7% and 67% of reduction in GTVs at QS2 (172.6 cc, *P* = .02) and at QS3 (117.4 cc, *P* = .01), respectively (Table 2). Overall objective response showed RECIST SD in 2 sites (25%) or PR in 6 sites (75%) after QS1, and PR in all 8 sites (100%) after QS2. There were no patients with RECIST CR on CT-simulation scan at QS3. Figure 2 shows an example of GTVs at each Quad shot in 2 patients (Fig 2A-C, metastatic papillary thyroid carcinoma on chest wall; Fig 2D-F, recurrent urothelial carcinoma in cystectomy bed).

No grade 3 or higher acute toxicity from quad shot was observed in patients. One patient reported grade 2 fatigue

after QS2, but rapid metastatic disease progressions at nonquad shot sites also occurred while this patient reported fatigue. There was 1 patient with grade 1 diarrhea after QS1 to recurrent urothelial carcinoma at cystectomy bed but no further diarrhea after QS2 and QS3.

Six patients have died since their last quad shot RT (3 after QS1, 1 after QS2, and 2 after QS3). One patient was lost to follow up after QS3. The 5 remaining patients are alive as of May 2021 (4-18 months since QS1). All patients maintained notable symptom(s) relief after quad shot(s) until their last contact or death.

Discussion

For elderly or frail patients with nonosseous metastatic/recurrent cancer, surgery or systemic therapy (chemotherapy or biologic target therapy) may not be possible, and RT may be the only palliative care for

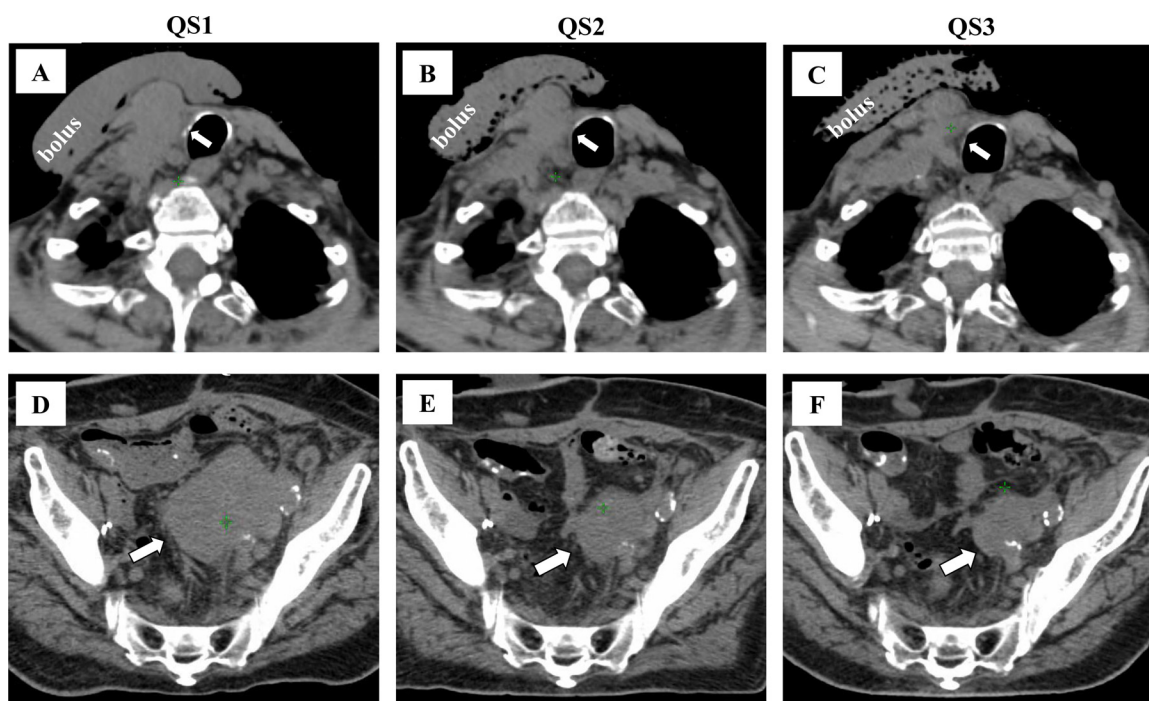


Fig. 2 (A-C) Computed tomography-simulation scans for QS1, QS2, and QS3 in a patient with metastatic papillary thyroid carcinoma. D-F, Recurrent urothelial carcinoma in cystectomy bed. White arrows indicate gross tumor. *Abbreviation:* QS = quad shot.

presenting symptoms. Short overall treatment time, rapid symptom relief, and minimum toxicity are important aspects of palliative RT for such physically and emotionally exhausted patients.

In this case series, all 12 elderly or frail patients complied and tolerated well the 2 consecutive days course of QS1. Rapid notable symptom response was observed in all 12 sites, including 4 complete resolution of symptoms within 2 to 3 weeks after QS1 (Fig 1). Such rapid subjective symptom response after QS1 can be explained by a significant objective response (42.7% of mean GTV reduction) after QS1 (Fig 2). Like the results of quad shot to advanced pelvic or head and neck cancer,^{4-7,9} we observed further reduction of residual symptoms and GTVs with additional quad shots (QS2-QS3) to nonosseous metastatic/recurrent sites in our elderly or frail patients. Of the 8 sites that received QS3, all achieved objective radiographic response, including interval stability (RECIST SD, 2 sites) and shrinkage (RECIST PR, 6 sites) after QS1. Subsequent QS2 resulted in RECIST PR in all 8 sites (Table 2, Fig 2).

Interestingly, both subjective and objective responses from QS1 were observed regardless of malignant histology, including radioresistant low alpha-beta ratio cancers such as melanoma, urothelial carcinoma, thyroid carcinoma, and sarcoma. Although the number of cases is small and there is heterogeneity in the histology, the responses from quad shots for such low alpha-beta ratio cancers in this case series are comparable to the published data.⁹ Lee et al reported results from palliative quad shot using proton beam to 40 recurrent or metastatic sarcomas in various sites (lung, trunk, abdomen, and extremities) showing a 70% subjective palliative response and durable local sarcoma control (11 months of median local progression-free survival).⁹ Radiobiologic experiments have suggested that increasing the dose per fraction using hypofractionation may treat those low alpha-beta ratio cancers more effectively than delivering smaller conventionally fractionated doses (1.8~2.0 Gy/fx).^{10,11} Thus, radiobiologic advantages from hypofractionated doses

(3.5-3.7 Gy/fx) in accelerated schedule (twice daily for 2 consecutive days) of quad shot RT can account for rapid subjective and objective responses in low alpha-beta ratio cancers after QS1 in this report.

The favorable acute toxicity profile after quad shot for the elderly or frail patients in this report is encouraging. No patients developed acute grade 3 or higher acute toxicity after quad shot. Only 2 acute toxicities were reported after QS1. Grade 2 fatigue occurred in a patient whose metastatic melanoma at nonirradiated sites rapidly progressed, albeit with local symptom relief after QS1. Another patient reported grade 1 diarrhea after QS1 to a large recurrent urothelial carcinoma in the cystectomy bed (Fig 2D), but no further diarrhea from subsequent QS2 and QS3. Furthermore, favorable toxicity after quad shot to elderly or frail patients in this case series is comparable to the reported low (6%-9%) gastrointestinal, oral mucosal, or dermatologic toxicity in patients with pelvic or head and neck malignancies after palliative quad shot RT.⁴⁻⁷ A cyclically hypofractionated RT schedule permits radiation target revision for QS2 and QS3 to account for decreased GTVs from previous quad shot (Fig 2). The adaptive replanning RT allows less radiation exposure to normal tissue as anatomic shifts may occur with decreased GTVs. Four-week intervals between each quad shot may also allow the early-responding normal tissue to recover from acute mild (grade 1-2) radiation toxicities before subsequent quad shot, and prevent developing grade 3 or higher toxicities.

Usually, repeating diagnostic imaging is not routinely performed once patients achieve local symptom relief after palliative care. Thus, objective response after QS3 has not been extensively evaluated. Due to medical necessity, however, 3 patients in this report had diagnostic imaging after QS3 that included irradiated sites. Figure 3 shows a near CR on magnetic resonance imaging at 3 months after QS3 to adenocarcinoma of the rectum. Positron emission tomography-CT scans at 3 to 4 months after QS3 in the other 2 patients demonstrated stable recurrent/metastatic tumors since QS3. These findings

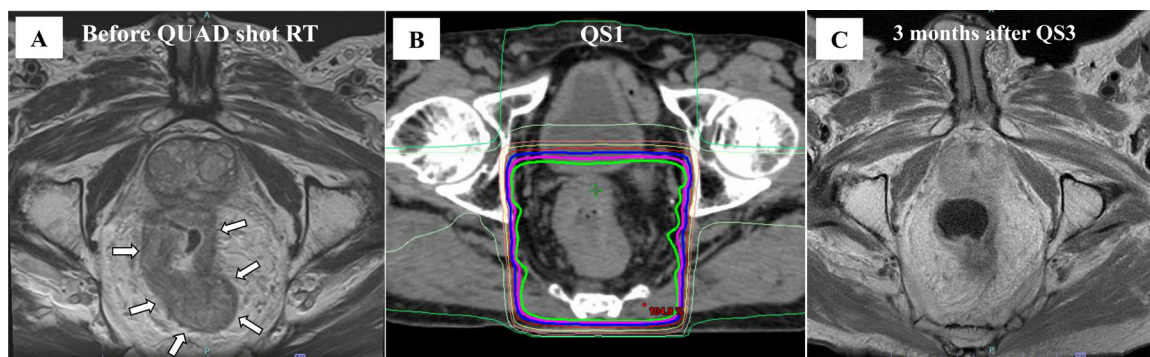


Fig. 3 A 92-year-old patient with dementia and adenocarcinoma of the rectum (white arrows) achieved partial symptom (constipation and rectal bleeding) relief after first quad shot and complete symptom resolution after third quad shot. Magnetic resonance imaging at 3 months after third quad shot shows near complete resolution of tumor. *Abbreviations:* QS = quad shot; RT = radiation therapy.

suggest that 3 or more quad shots to nonosseous metastatic/recurrent cancers may offer rapid symptom palliation, and also durable local tumor control in elderly or frail patients.

Although our data demonstrated rapid and durable symptom palliation from quad shot to nonosseous metastatic/recurrent malignancies in elderly or frail patients, this report has some limitations. Most importantly, only a small number of patients with mixed histology were evaluated in this report. Retrospective case collection in a rural community clinic setting may account for such small numbers and heterogeneous histology in this report. Because of these limitations, further investigation with a collaboratively collected large number of nonosseous metastatic/recurrent malignancies in elderly or frail patients using palliative quad shot is warranted.

Conclusion

For elderly or frail patients with nonosseous metastatic/recurrent cancer in this case series, the quad shot was a well-tolerated palliative RT consisting of short overall treatment time. Quad shot provided rapid and durable symptom relief regardless of cancer histology and caused only mild acute toxicity, all of which are vital in palliative care.

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