Palliative Care Rounds

The Use of "QUAD Shot" in Anal Canal Squamous Cell Carcinoma: A Case Study With Review of the Literature

Neil Chevli, MD, Gary D. Lewis, MD, and Todd A. Swanson, MD, PhD
Department of Radiation Oncology, University of Texas Medical Branch at Galveston, Galveston, Texas, USA

Abstract

Context. Patients with locoregional anal carcinoma who do not qualify for standard definitive chemoradiation are candidates for a short course of palliative hypofractionated radiotherapy such as QUAD Shot.

Methods. A 57-year-old man with massive locoregional squamous cell carcinoma of the anal canal was treated with QUAD Shot (14.8 Gy in four fractions over two consecutive days) repeated every four weeks for a total of two courses.

Results. He reported symptomatic relief following each course of radiation. In regard to his first QUAD Shot, his pain was 10/10 in severity at the time of admission and 4/10 at the time of discharge. In regard to his second QUAD Shot, his pain was 8/10 at the time of admission and 0/10 at the time of discharge. He did not experience any treatment-related toxicity. He passed away 15 weeks after the first course.

Conclusion. QUAD Shot is both efficacious and safe for palliation in patients with anal carcinoma. J Pain Symptom Manage 2019;57:341–345. © *2018 Published by Elsevier Inc. on behalf of American Academy of Hospice and Palliative Medicine.*

Key Words
QUAD Shot, palliative radiotherapy, anal cancer

Introduction

Since the introduction of the Nigro protocol,[1] concurrent chemoradiation has replaced colostomy-inducing surgery as the standard of care for patients with locoregional anal squamous cell carcinoma. For patients with metastatic disease, concurrent chemoradiation is also given to palliate symptoms associated with local disease involvement including pain, bleeding, discharge, and rectal dysfunction.[2,3] Although chemotherapy regimens differ, the radiation course typically consists of 45 Gy delivered in 25 fractions followed by a boost of 10 to 14 Gy in five to seven fractions over a period of six to seven weeks.[4] Improved survival is achieved with even higher doses of radiation, but radiation-induced complications limit dose escalation.[5]

Standard course concurrent chemoradiation for anal carcinoma is harsh and often requires treatment interruption.[6] Acute toxicities include cytopenias, dermatitis, proctitis, diarrhea, and dysuria.[7] These acute side effects spontaneously resolve a few weeks after completing treatment. In addition, late side effects develop many months after treatment and include perineal skin atrophy, fecal incontinence, urinary incontinence, dyspareunia, and impotence.[7,8]

Occasionally, a patient may be unable to undergo the standard full course of chemoradiation for a variety of reasons. Typical situations include a patient with poor performance status who cannot tolerate the acute toxicities, poor prognosis where the acute toxicities interfere with quality of life goals, or logistical issues involving daily transportation to a radiotherapy center. In such situations, an abbreviated course of radiation may be administered for palliation with the goal of minimizing both toxicity and time and effort spent in treatment.[9]

Address correspondence to: Dr. Todd A. Swanson, MD, PhD, Department of Radiation Oncology, University of Texas Medical Branch at Galveston, 301 University Blvd., Galveston, TX 77555, USA. E-mail: taswanso@utmb.edu

Accepted for publication: October 29, 2018.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2018.10.512

One regimen of short-course radiation that has been used in palliative settings is known as the "QUAD Shot." It is named as such because each cycle consists of four fractions delivered over a two-day period.[10] This regimen has been well characterized in the treatment of head/neck and gynecologic cancers. However, there are no published studies specifically documenting the effectiveness of the QUAD Shot for anal carcinoma. We herein present the first such published case.

Case Description

A 57-year-old heterosexual man presented to the emergency room in January 2017 for an open wound on his buttocks (Table 1). He began developing anal and genital warts in mid-2016, and these lesions ruptured in November 2016, resulting in continuous painful purulent foul-smelling discharge. He was initially reluctant to seek medical attention because he did not have insurance coverage, but at the time of presentation, he had recently been approved for Medicaid.

He was admitted for systemic inflammatory response syndrome. Physical examination demonstrated bilateral perianal and gluteal masses and a right sided abscess with purulent odoriferous drainage. CT of the pelvis revealed a large posterior skin defect at the level of the coccyx with multiple subcutaneous tracts, a lobulated perianal mass measuring $8.5 \times 6.4 \times 4.2$ cm with central hypodensity suggesting necrosis or superinfection, and bilaterally enlarged inguinal and internal iliac lymph nodes up to 1 cm. CT of the thorax and abdomen and MRI of the brain were negative for metastasis. HIV antibody testing was negative. General surgery performed a diverting colostomy and biopsied the perianal mass. Biopsy revealed well-differentiated squamous cell carcinoma, p16 negative. He was subsequently discharged with outpatient follow-up appointments with medical oncology and radiation oncology.

Although he did not show up to his outpatient appointments with medical oncology, he did show up to his radiation oncology appointment in February 2017. Subjectively, his symptoms were unchanged and objectively his Karnofsky Performance Status (KPS) was 70%. PET scan detected no distant metastatic disease. His anal canal squamous cell carcinoma was staged as cT3N3M0, IIIB (AJCC 7), and it was recommended that he proceed with curative chemoradiation.

In March 2017, he returned to the emergency department for pain. CT scan showed the perianal mass had increased to 11 cm. He was discharged with pain medications and follow-up appointments. In April 2017, he returned to the emergency department with systemic inflammatory response syndrome. His pain was reported as 10/10 in severity, and his KPS was 60%. Regarding his activities of daily living, he was able to feed himself, but due to his pain, he required assistance with bathing and using the toilet. Because of his history of missed clinic appointments, providing chemotherapy and delivering an extended course of radiotherapy were determined to be implausible and unsafe. After discussion between palliative medicine, radiation oncology, and medical oncology, a consensus was reached to administer a short course of radiation as an inpatient. He was treated with external beam radiation therapy to 14.8 Gy in four fractions over the course of two days (i.e., QUAD Shot) with the potential to repeat this same course up to two additional times with four weeks between each course. He was subsequently discharged to a nursing home. At the time of discharge, his pain was reported as 4/10 in severity and his KPS was 50%.

In mid-May, he was readmitted to receive his second course of QUAD Shot. At the time of admission, his pain was 8/10 in severity and his KPS was 50%. At the time of discharge, his pain was reported as 0/10 in severity.

In late-May, he was admitted for anemia and received a transfusion. On admission, his pain was reported as 4/10 in severity. He had achieved significant improvement in his activities of daily living at this time—he was able to bathe, use the toilet, and feed independently. Although he was not due for his final course of QUAD Shot for another week, he was seen

Table 1
Summary of Clinical Events

Date	Event	Performance Status	Treatment	Post-RT Status
Mid-2016	Developed anal and genital warts			
Nov. 2016	Lesions ruptured			
Jan. 2017	Admitted for SIRS and diagnosed with SCC			
Feb. 2017	Radiation Oncology outpatient appointment	KPS 70%		
Mar. 2017	Returned to ED for pain			
Apr. 2017	Admitted for SIRS	Pain 10/10 KPS 60%	QUAD Shot	Pain 4/10 KPS 50%
May 2017	Planned admission for RT	Pain 8/10 KPS 50%	QUAD Shot	Pain 0/10 KPS 50%
May 2017	Admitted for anemia	Pain 4/10	Declined	
Aug. 2017	Expired from disease			

RT = radiotherapy; SIRS = systemic inflammatory response syndrome; SCC = squamous cell carcinoma; KPS = Karnofsky Performance Status; ED = emergency department.

by radiation oncology as an inpatient to discuss his therapy. At that time, he opted for hospice and declined the final course of QUAD Shot. He passed away in August 2017 from disease.

Comment

Here, we have presented the case of a 57-year-old man with stage cT3N3M0, IIIB anal carcinoma who was treated palliatively with a QUAD Shot because he could not logistically receive the standard course of curative chemoradiation. QUAD Shot is a form of hypofractionated radiotherapy that is used in many malignancies, including pelvic and head/neck cancers.[11,12]

The first published report of hypofractionated radiotherapy used for palliation was in 1959 for patients with breast cancer[13] (Table 2). These patients received 12.5 Gy per day for two days. Because the initial results seemed favorable, numerous follow-up studies examined different hypofractionation courses for breast cancer ranging from 8 to 12.5 Gy per fraction, per day delivered daily or weekly with a maximum of four fractions with cumulative doses ranging from 16 to 40 Gy.[18–22] Hypofractionated regimens were subsequently examined for other cancers including the head/neck.[23] However, because the consensus was that these regimens caused excessive late toxicity, dose-escalated hypofractionated radiotherapy was abandoned for the next decade.

A similar hypofractionation regimen was first evaluated for gynecologic cancers in 1979 in a study at MD Anderson Cancer Center that used split-course whole pelvic radiation with 10 Gy in one fraction repeated every three to four weeks for up to three courses.[14] This regimen showed good efficacy with minimal acute complications. In a follow-up study, patients with pelvic malignancies were treated with chemoradiation consisting of misonidazole and split-course radiation at a dose of 10 Gy in one fraction repeated every four weeks for up to three courses.[15] This regimen showed good disease control but an unacceptably high rate of late gastrointestinal toxicity. In an attempt to replicate the efficacy of these hypofractionated regimens but also eliminate the high rate of late toxicity, the QUAD Shot was invented. RTOG 85-02 was a split-course accelerated hypofractionation schedule where 3.7 Gy was delivered twice a day for two days and repeated every four weeks for up to three courses for a maximum total of 44.4 Gy.[11] This course was shown to be both safe and effective in locally advanced pelvic malignancies including gynecological, colorectal, and genitourinary[11] with an acceptable rate of late toxicity.[24]

Table 2
Summary of Relevant Split-Course Accelerated Hypofractionated Radiotherapy Studies

Pub Year (Citation)	Cancer Type	Palliative Regimen
1959[13]	Breast	12.5 Gy/fx, 2 fx (2 days)
1979[14]	Gynecologic	10 Gy/fx, 1 fx; 3 courses
1987[15]	Pelvic	10 Gy/fx, 1 fx; 3 courses; concurrent misonidazole
1989[11]	Pelvic	3.7 Gy/fx, 4 fx (2 days); 3 courses
2007[16]	Pelvic, head and neck	3.7 Gy/fx, 4 fx (2 days); 3 courses; concurrent paclitaxel
2012[17]	Pelvic	3.5–4.5 Gy/fx, 4 fx (2 days); 3 courses

Because of these promising results, QUAD Shot was soon extrapolated to other malignancies, most notably head/neck cancers. Both a phase I-II trial and a phase II trial comprised of 39 and 30 patients respectively reported palliative efficacy of 85% with acceptable levels of toxicity [10,12]. Furthermore, a retrospective study comparing QUAD Shot to four other palliative regimens for head/neck cancer showed it had the lowest grade 3 toxicity.[25] More recently, QUAD Shot was extrapolated to other malignancies and even other modalities. Proton QUAD Shot with curative intent was shown to be feasible for sarcomas in a retrospective study involving 22 patients at Memorial Sloan Kettering Cancer Center, but future prospective testing is needed to determine the relative efficacy and safety of this treatment compared with other therapeutic options.[26]

Since the advent of the QUAD Shot, there have been multiple attempts to improve upon this regimen. The first attempt was an extension of RTOG 85-02 where the final 136 patients were randomized to intervals between courses of four weeks and two weeks. Because the two-week interval showed a trend toward increased acute toxicity with no difference in response rate,[27] this idea was subsequently abandoned. The next attempt was a single-arm prospective study of 20 patients with advanced pelvic and head/neck cancer who received the radiosensitizer paclitaxel in addition to QUAD Shot.[16] This showed a good response rate, symptom palliation, and low toxicity. To further elucidate the benefit of adding concurrent chemotherapy to QUAD Shot, a retrospective study was performed at Memorial Sloan Kettering Cancer Center involving 75 patients with head/neck cancer, 22 of which received concurrent systemic chemotherapy.[28] Although the number of QUAD Shot cycles received was associated with palliative response, administration of concurrent systemic chemotherapy was not. In contrast, a more recent study involving 21 patients who all received QUAD Shot with radiosensitizing chemotherapy found that palliation of the presenting symptom was achieved in all patients who finished three courses

and no grade 3 toxicity occurred.[29] Because of the mixed results from these prior studies, it remains unclear whether the addition of concurrent chemotherapy to QUAD Shot is beneficial.

The QUAD Shot was invented in the era of two-dimensional radiation techniques. Therefore, it is plausible that with three-dimensional conformal techniques, a higher dose can be used with greater efficacy and acceptable toxicity. To test this theory, a phase I dose escalation study evaluating 3.5, 4.0, and 4.5 Gy twice a day for two days for a total of 14, 16, and 18 Gy, respectively, in 27 patients with locally advanced or metastatic pelvic cancer showed an 89% response rate, no grade 3–4 acute toxicity, and no late toxicity at a median follow-up of six months.[17] Although a phase II study on this topic was planned, our review of the literature found no further published studies examining QUAD Shot or any modification of QUAD Shot.

In conclusion, the use of the QUAD Shot for palliation in this 57-year-old man provided meaningful pain relief. Split-course, accelerated hypofractionated radiotherapy is a good option for patients with anal carcinoma who for whatever reason cannot undergo the standard six- to seven-week course of definitive chemoradiation. Further studies involving modifications to this regimen are warranted to find a regimen that is the least time intensive and still provides the greatest palliation with the least toxicity.

Disclosures and Acknowledgments

No funding was received for this work, and the authors declare no conflicts of interest.

References

1. Nigro N, Vaitkevicius V, Considine B. Combined therapy for cancer of anal-canal: a preliminary report. Dis Colon Rectum 1974;17:354–356.

2. Benson AB III, Arnoletti JP, Bekaii-Saab T, et al. Anal carcinoma, version 2.2012: featured updates to the NCCN guidelines. J Natl Compr Canc Netw 2012;10:449.

3. Spencer K, Parrish R, Henry A. Palliative radiotherapy. BMJ 2018;360:k821.

4. Gunderson LL, Winter KA, Ajani JA, et al. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol 2012;30:4344–4351.

5. Martin FT, Kavanagh D, Waldron R. Squamous cell carcinoma of the anal canal. Surgeon 2009;7:232–237.

6. Salama JK, Mell LK, Schomas DA, et al. Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: a multicenter experience. J Clin Oncol 2007;25:4581–4586.

7. Milano MT, Jani AB, Farrey KJ, et al. Intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys 2005;63:354–361.

8. Bentzen AG, Balteskard L, Wanderås EH, et al. Impaired health-related quality of life after chemoradiotherapy for anal cancer: late effects in a national cohort of 128 survivors. Acta Oncol 2013;52:736–744.

9. Lutz ST, Jones J, Chow E. Role of radiation therapy in palliative care of the patient with cancer. J Clin Oncol 2014;32:2913–2919.

10. Spanos W, Guse C, Perez C, et al. 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;17:659–661.

11. Paris KJ, Spanos WJ, 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;25:657–660.

12. Cochran DQ, Holtz S, Powers WE. The rapid palliative treatment of breast carcinoma: a preliminary report. AJR Am J Roentgenol 1959;81:479.

13. Horrigan WD, Atkins HL, Tapley ND. Massive-dose rapid palliative radiotherapy: a preliminary report. Radiology 1962;78:439–444.

14. Spanos WJ, Wasserman T, Meoz R, et al. Palliation of advanced pelvic malignant disease with large fraction pelvic radiation and misonidazole: final report of rtog phase I/II study. Int J Radiat Oncol Biol Phys 1987;13:1479–1482.

15. Spanos WT, Clery M, Perez CA, et al. Late effect of multiple daily fraction palliation schedule for advanced pelvic malignancies (RTOG 8502). Int J Radiat Oncol Biol Phys 1994;29:961–967.

16. Carrascosa LA, Yashar CM, Paris KJ, et al. Palliation of pelvic and head and neck cancer with paclitaxel and a novel radiotherapy regimen. J Palliat Med 2007;10:877–881.

17. Caravatta L, Padula GDA, Macchia G, et al. Short-course accelerated radiotherapy in palliative treatment of advanced pelvic malignancies: a phase I study. Int J Radiat Oncol Biol Phys 2012;83:e627–e631.

18. Stoll BA. Rapid palliative irradiation of inoperable breast cancer. Clin Radiol 1964;15:175–178.

19. Atkins HL. Massive dose technique in radiation therapy of inoperable carcinoma of the breast. AJR Am J Roentgenol 1964;91:80.

20. Edelman AH, Holtz S, Powers WE. Rapid radiotherapy for inoperable carcinoma of the breast: benefits and complications. AJR Am J Roentgenol 1965;93:585.

21. Montague ED. Physical and clinical parameters in the management of advanced breast cancer with radiation therapy alone. AJR Am J Roentgenol 1967;99:995.

22. Atkins HL. Massive single dose, weekly fractionation technique in treatment of head and neck cancer: preliminary report. AJR Am J Roentgenol 1964;91:50.

23. Boulware RJ, Caderao JB, Delclos L, Taylor Wharton J, Peters LJ. Whole pelvis megavoltage irradiation with single doses of 1000 rad to palliate advanced gynecologic cancers. Int J Radiat Oncol Biol Phys 1979;5:333–338.

24. Corry J, Peters LJ, Costa ID, et al. The 'QUAD SHOT'- a phase II study of palliative radiotherapy for incurable head and neck cancer. Radiother Oncol 2005;77:137–142.

25. 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: 1586–1591.

26. Patel S, Anderson ES, Kelly C, et al. Proton quad shot rt for palliation in patients with advanced sarcoma. Int J Radiat Oncol Biol Phys 2017;99:E756–E757.

27. Spanos WJ, Perez CA, Marcus S, et al. Effect of rest interval on tumor and normal tissue response- a report of phase III study of accelerated split course palliative radiation for advanced pelvic malignancies (RTOG-8502). Int J Radiat Oncol Biol Phys 1993;25:399–403.

28. Lok BH, Jiang G, Gutiontov S, et al. Palliative head and neck radiotherapy with the RTOG 8502 regimen for incurable primary or metastatic cancers. Oral Oncol 2015;51: 957–962.

29. Gamez ME, Agarwal M, Hu KS, Lukens JN, Harrison LB. Hypofractionated palliative radiotherapy with concurrent radiosensitizing chemotherapy for advanced head and neck cancer using the "QUAD-SHOT Regimen". Anticancer Res 2017;37:685–691.