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Case Report

Palliative Radiation Therapy of Symptomatic Recurrent Bladder Cancer

Sun K. Yi[1], Mark Yoder[2], Ken Zaner[2], MD, PhD, and Ariel E. Hirsch[1], MD

From: Departments of [1]Radiation Oncology and [2]Medical Oncology Boston University Medical Center, Boston, MA.
Yi[1] is a fourth year medical student, Department of Radiation Oncology, Boston University School of Medicine, Boston, MA.
Yoder[2] is a Nurse Practioner, Department of Hematology/ Oncology, Boston University Medical Center, Boston, MA
Dr. Zaner[2] is Associate Professor of Medicine, Department of Hematology/ Oncology, Boston University Medical Center, Boston, MA.
Dr. Hirsch[1] is Assistant Professor, Director of Education, Department of Radiation Oncology, Boston University Medical Center, Boston, MA; and Assistant Radiation Oncologist, Massachusetts General Hospital, Harvard Radiation Oncology Program, Boston, MA.
Address Correspondence:
Ariel E. Hirsch, MD
Department of Radiation Oncology
Boston University Medical Center
830 Harrison Avenue
Moakley Building-Lower Level
Boston, MA 02118
E-mail: ariel.hirsch@bmc.org
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Background: Palliative radiation therapy (RT) is an established tool in the management of symptoms caused by malignancies. RT is effective at palliating both locally advanced and metastatic cancer, including related symptoms of pain, bleeding, or obstruction. Most data on palliative RT is in regard to its use in the treatment of painful bone metastases. There are also data that support RT palliation for locally advanced or recurrent rectal, prostate, and gynecological cancers. With regard to bladder cancer there is some evidence of the benefit of palliative RT for the control of urinary symptoms and hematuria; however, there is little evidence for the use of palliative RT for pain associated with locally recurrent bladder cancer. We report a case of locally advanced recurrent bladder cancer which was refractory to medical pain management, and was found to be highly responsive to palliative RT.

Case Report: An 80-year-old woman with recurrent bladder cancer and intractable pelvic pain refractory to oral and transdermal pain medications, received palliative pelvic RT to a dose of 50 Gy (5000 cGy) in 25 fractions with complete resolution of pain. The patient was originally found to have dysuria, frequency, and hematuria, secondary to an invasive high grade transitional cell carcinoma of the bladder with an adenocarcinoma component, AJCC pT2b N1 M0 Stage IV, for which she underwent a radical cystectomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, partial vaginectomy, and ileal conduit reconstruction. After undergoing 4 cycles of adjuvant chemotherapy, the patient did well for 5 months with no evidence of symptomatic, clinical, or radiographic recurrence of disease. Repeat staging CT of the abdomen and pelvis confirmed tumor recurrence in the left pelvis. The patient was treated with another course of chemotherapy and pain was managed with relatively low doses of opioid medication (25mcg transdermal fentanyl patch, and oxycodone 5mg bid). However at the fourth month, there was rapid escalation of severe pain with the patient becoming bed bound due to pain with an associated decrease in ambulation and anorexia. Ultimately a pain medication regimen of 200mcg transdermal fentanyl patch q2 days, oxycontin 20mg bid, oxycodone 5 – 10mg q 4 hours, ibuprofen 400mg q 8 hours, and gabapentin 600mg TID was not effective in controlling pain. The patient was then referred to Radiation Oncology 6 months after the pain initially began for evaluation. She received a total of 5000cGy over 25 fractions to a small pelvis field over 5 weeks and reported complete pain resolution. She was able to decrease pain medications, increase overall activity, and gain significant improvement in sleep quality and appetite even early on in the course of her radiation therapy.

Conclusions: Palliative radiation therapy has been well studied in the setting of bone metastases and treatment of hematuria for locally advanced bladder cancer. There is little data that we are aware of on the use of RT for pain control with patients that have recurrent, locally advanced bladder cancer. We have presented a case in which an excellent outcome in pain control was seen for a patient with medically unmanageable pain. RT is an excellent option for pain management in recurrent bladder cancer and should be offered to patients whose pain is not otherwise optimally controlled. Palliative RT is an important component in the multimodality approach to cancer pain management and optimization of quality of life.

Key words: palliation, bladder cancer, radiation therapy

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An 80-year-old woman was initially diagnosed with a transitional cell carcinoma (TCC) with an adenocarcinoma component of the bladder in February 2005 upon evaluation by cystoscopy and transurethral resection, after complaining of dysuria, frequency, and hematuria. In March 2005, the patient underwent radical cystectomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, partial vaginectomy, and ileal conduit reconstruction for a 3 x 2.5 x 1.2cm, invasive high grade TCC with a major glandular differentiated (adenocarcinoma) component, found extending through the muscular wall (2mm from serosal surface). One out of 8 dissected lymph nodes were positive for metastatic TCC from the right external iliac and obturator region (AJCC Pathologic Stage IV pT2b N1 M0).

The patient was seen by medical oncology in April 2005 following her surgery and received adjuvant cisplatinum and gemcitabine chemotherapy for 4 cycles, which the patient tolerated well. Upon completion of chemotherapy, a CT of the abdomen and pelvis was taken in August 2005, and showed no evidence for recurrence. The patient reported doing well until December 2005 when she reported left lower quadrant pain.

The patient described the pain as "pressure-like" in quality, radiating to the low back, and was made worse with standing and relieved with sitting or lying. The patient reported gradual worsening of the pain over time, which was found to be exacerbated by eating and associated with constipation. While hospitalized for increasing pain, the patient underwent a repeat CT scan of the abdomen and pelvis, that showed soft tissue masses located within the left pelvis that were suggestive of tumor recurrence.

The patient subsequently received Taxotere x 3 cycles in the months of February and March of 2006. The patient was initially placed on morphine elixir for pain management and after 1 dose experienced severe epigastric pain, vomiting, and chest pain resulting in hospitalization. A complete cardiac workup was negative and the symptoms were thought to be due to the side effects from the morphine elixir. The patient was discharged from the hospital on morphine sustained release tablets 15mg PO BID and oxycodone 5mg PO BID PRN for breakthrough pain.

The patient was seen in the medical oncology clinic for pain reevaluation 1 week following her discharge. At that time, she reported restlessness, unsteadiness on her feet, and picking at things in the air. This was thought to be related to the morphine and the sustained release morphine was discontinued. She was then started on 25mcg fentanyl transdermal patch changed q 48 hours. The patient's pain was closely monitored over the subsequent few months with gradual titration of fentanyl transdermal patch to 75mcg q2d and oxycodone was increased to 10mg PO q4-6h PRN for breakthrough pain.

A repeat CT of the abdomen and pelvis in May 2006 showed interval worsening of her left-sided pelvic soft tissue mass without evidence of bony abnormality (Fig. 1). She was now starting to experience severe pain without relief even with the increase in Fentanyl dose to 150mcg q2d. At this point the patient reported that the pain was interfering with her sleep and appetite. Additionally, at that time she had become virtually bed bound, because it was too painful to walk leading to a subsequent decrease in physical strength, and she required weekly visits to the oncology clinic for hydration.

The patient was then referred to the radiation oncology department in June 2006, at which point she was on duragesic fentanyl patch 200mcg q2d, gabapentin 300mg PO QID, ibuprofen 400mg q6h, and oxycontin 20mg PO BID for severe (7/10 on the numeric pain scale) pain with no relief at all.

Radiation therapy commenced on June 1, 2006, for 25 fractions to a total dose of 5000 cGy to a small pelvis field (Fig. 2). After the initial 2000 cGy out of total 5000 cGy the patient reported improvement in pain. The patient was able to decrease her fentanyl patch to 150mcg, without need for oxycontin. With subsequent radiation treatment the patient continued to report increasing pain relief, increased activity, improvement in sleep, and improved appetite. Halfway through the course of radiation, the patient was able to decrease her fentanyl patch to 125 mcg with no need for breakthrough pain medication. At that point in time, the patient denied any pelvic pain (0/10). Upon completion of the 25 fractions of radiation, the patient continued to report no pain (0/10) and was able to decrease her fentanyl patch to 75 mcg, with no need for breakthrough pain medication.

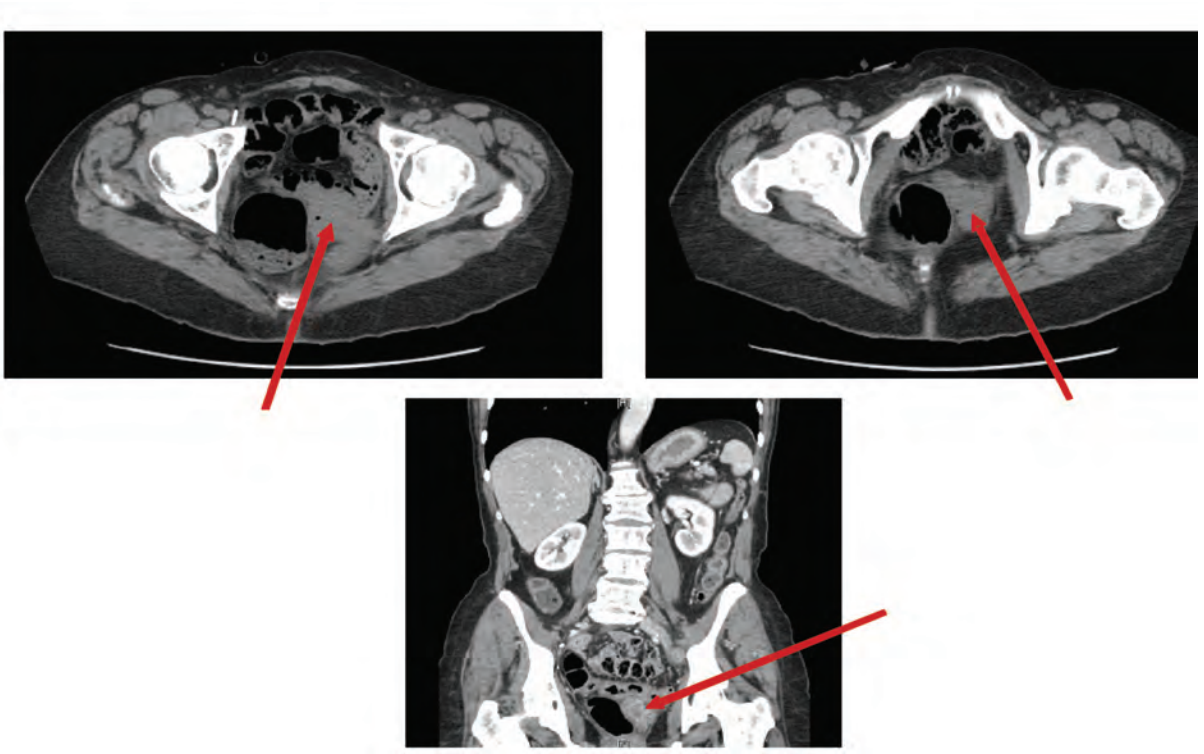

Fig. 1. *May 2006 CT scan of abdomen and pelvis showing large soft tissue densities in the left pelvis causing mass effect of the rectum (tumor indicated with red arrows).*

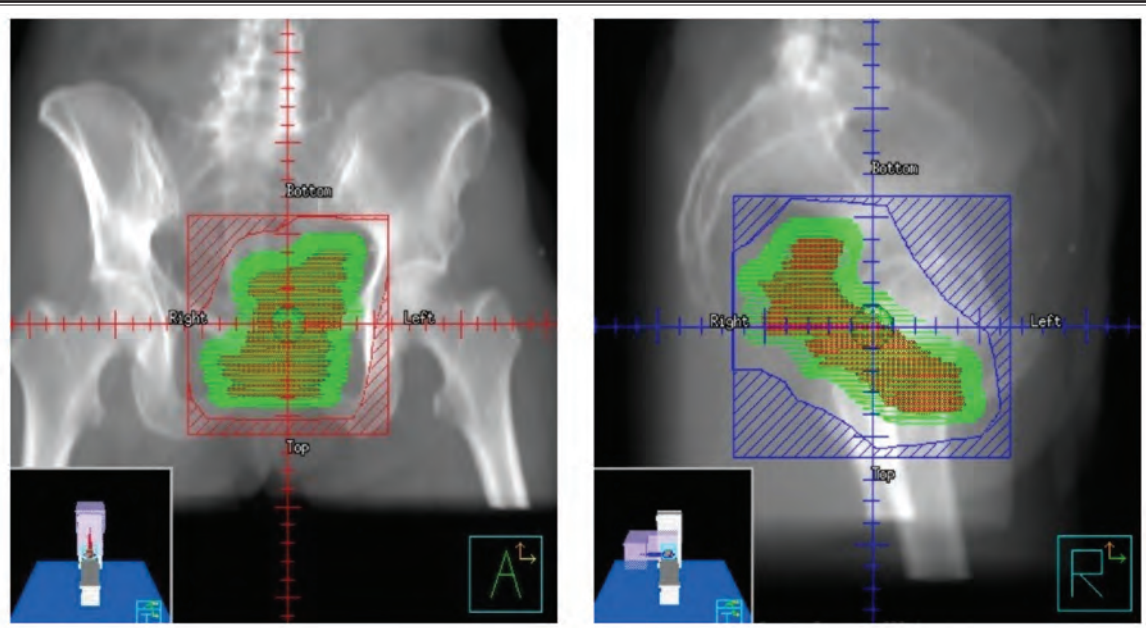

Fig. 2. *AP and lateral radiation treatment fields of the pelvis with tumor volume in red and clinical target volume in green.*

Discussion

Pain is one of the most feared symptoms encountered by patients who suffer from cancer (1). The Radiation Therapy Oncology Group (RTOG) has reported that many physicians, as high as 83% of RTOG-affiliated physicians according to 1 recently taken survey, believe that pain is undertreated in cancer patients for a variety of reasons including inadequate pain assessment, underreporting of pain by the patient, fear of opioid dependence, as well as other socio-legal issues (2). The American Pain Society (APS) has provided well-documented guidelines for pain management of the cancer patient. Much of the guidelines has been geared toward the pharmacological treatment of pain associated with cancer including the use of NSAIDS, opioids, and anticonvulsant medications. Palliative RT is only briefly mentioned in the APS guideline for management of cancer pain (3). Recent APS recommendations have stressed the importance of employing a multimodality treatment approach to the treatment of cancer pain (4).

With respect to palliative RT in the current literature, there are well-established data that describe the benefit of palliative radiation therapy for pain, bleeding, or obstruction associated with recurrent, locally advanced, or metastatic cancer (2,5,6). RT for the palliative treatment and management of painful bone metastases has been well studied and has been shown to be extremely effective reducing pain in up to 90% of patients (7-11). Currently external beam radiation therapy is the standard of care for treating patients suffering from bone metastases, and recent studies looking at radiopharmaceuticals, such as strontium-89, have also shown a benefit in pain management (12).

With regard to the palliative management of pelvic malignancies, there are data that suggest a benefit of palliative RT treatment for locally advanced tumors, particularly rectal and gynecological cancers. Studies that have evaluated the benefit of palliative RT for rectal cancer have shown statistically significant improvement in pain control for patients suffering from locally advanced disease (13-16). Improvement in pain control has also been found with palliative RT in patients with locally advanced gynecological malignancies including cervical, endometrial, and ovarian cancers (17-20). Furthermore, there are data that have shown palliative RT to be effective in the pain relief of patients suffering from advanced, hormone-refractory prostate cancer (21, 22).

In terms of palliative RT for the treatment of symptoms associated with recurrent and locally advanced bladder cancer, most of the literature describes improvement in malignancy-associated hematuria (23-25). There have been few studies that have specifically addressed the role of RT for pain relief in patients who suffer from recurrent bladder cancer. In 1 study performed by Srinivasan et al (26), a comparison of 2 radiotherapy regimens for the treatment of advanced bladder cancer, in which one group received 45 Gy over 12 fractions compared to 17 Gy in 2 fractions, showed pain improvement in both groups, 37% and 73%, respectively.

In our case, the patient's gradual worsening of pain was initially managed with standard medical management using opioids. Once the patient began to experience a marked escalation of pain, the pain medications were titrated accordingly by the guidelines provided by the APS and eventually included a regimen of opioids, NSAIDs, and an anticonvulsant. Her pain was found to be refractory to the increase in doses that were given to her at regular follow-up visits. Her pain control with medical management was particularly challenging as she had a number of opioid-related side-effects, including severe epigastric pain with only 5mg oral morphine elixir requiring hospital admission and full cardiac workup, visual hallucinations with extended release morphine tablets, and severe oxycodone-related drowsiness.

When the patient was evaluated in the radiation oncology department 6 months following the initiation of her pain, the patient reported severe, 7/10, "pressure-like" pain, which radiated to her lower back and was made worse with standing, but relieved with sitting or lying down. A CT scan of the abdomen and pelvis showed recurrent bladder cancer (Fig. 1) that was increasing in size and causing a mass effect to surrounding pelvic structures. In addition to gradually worsening pain, our patient suffered from worsening fatigue and inactivity, increased sleep disturbance, and decreased appetite secondary to her pain. Over the first 4 months immediately preceding referral to radiation therapy, the patient's pain symptoms were medically managed with variable results. However, over the 1 month just prior to referral to radiation, the symptoms rapidly escalated with severe pain leading to bed bound status and anorexia. She required weekly IV hydration to maintain nutritional status. The fentanyl dose had increased from 25 mcg to 200 mcg in this time period with little relief.

The patient received palliative RT to the left pelvis to a total of 5000 cGy in 25 fractions over 5 weeks to a small pelvis field (Fig. 2). After only the first 2 weeks of palliative RT the patient noted complete resolution of her pain, 0/10 in severity on the numeric pain scale. She reported minimal side effects directly attributable to RT, only reporting mild loose stools, which the patient actually welcomed since the constipation induced by increasing opioid intake was thought to be contributory to her postprandial abdominal pain and anorexia.

The mechanism of action for palliative RT and decreased pain symptoms is not completely understood at this time. It is believed that pain relief from external beam radiation may be secondary to the tumoricidal effect of RT on cells from advanced malignancy. It is thought that deceleration of tumor growth may allow for decreased surrounding edema, and therefore, decreased pressure on pain nerve fibers, thus allowing for decreased neuropathic or nociceptive pain stimulus. Others believe that RT-associated pain reduction occurs through alterations in the pain signaling pathways, and current animal model research is actively underway to elucidate the mechanisms for which cancer pain occurs and is altered by modalities such as RT (27, 28). While the mechanism of action remains unknown, RT has been shown to reduce cancer related pain, in addition to increasing the quality of life of patients who suffer from advanced cancer.

One goal of adequate pain management in patients with advanced cancer is to increase the Health-Related Quality of Life (HRQOL) for terminally ill patients (29). Palliative treatment for cancer patients is no longer regarded simply as the supportive means by which to reduce undesirable symptoms, but is better recognized as the World Health Organization defines it, "the active, total care of a person whose condition is not responsive to curative treatment" (30). That being said, it is important that we effectively treat pain and other unwanted symptoms associated with locally advanced cancers to improve the overall HRQOL of the patient.

Quality of life and its relationship to prognosis and/or survival rates has been studied in a variety of cancers and the data suggest that there may be a positive correlation between quality of life and prognosis/survival (31-34). When our patient was seen in the radiation oncology department, her HRQOL was poor due to her intractable pelvic pain, increasing fatigue and anorexia, and decreased ability to sleep and perform daily activities. She was confined to a wheelchair for mobility, and even getting up on the exam table was extremely challenging for her, as the pelvic pain was so severe. As our patient underwent palliative RT to her left pelvis, she reported complete pain resolution as well as overall increase in her HRQOL. We believe that early palliative RT included in the management of locally advanced recurrent bladder cancer is an important component of pain management and optimization of quality of life. More studies are needed to specifically evaluate the effectiveness of palliative RT for pain management and optimization of HRQOL in patients who suffer from recurrent, locally advanced bladder cancer.

Conclusion

Palliative radiation therapy has been well studied and there are well-established data for the benefit of palliative RT in the setting of bone metastases and locally advanced malignancy. Although there are studies that support the use of palliative RT for the treatment of hematuria for locally advanced bladder cancer, there are little data that we are aware of that have examined the use of RT for pain control with patients who have recurrent, locally advanced bladder cancer. We have presented a case in which an excellent outcome in pain control and increased HRQOL was seen for a patient with medically unmanageable pain. RT is an excellent option for pain management in recurrent bladder cancer and should be offered to patients whose pain is not otherwise optimally controlled, particularly in elderly patients who are sensitive to opioid therapy.

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