



Review Article

Practical aspects of palliative care & palliative radiotherapy in incurable cervical cancer

Reena George¹ & Bhavana Rai²

¹Department of Continuing Medical Education, Christian Medical College, Vellore, Tamil Nadu & ²Department of Radiotherapy & Oncology, Regional Cancer Centre, Postgraduate Institute of Medical Education & Research, Chandigarh, India

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Cervical cancer is the most common cause of cancer-related deaths among economically disadvantaged women. The symptoms of pain, discharge, constipation, foul smell, insomnia and depression can be controlled with inexpensive medicines such as oral morphine, maintenance oral metronidazole, antidepressants and laxatives. These medications should be prescribed according to the palliative care guidelines and titrated to the individual patient's clinical response, pathophysiology, and metabolic parameters. A hypothetical clinical scenario illustrates some aspects of pain and symptom management, inter-disciplinary palliative care, medical ethics and communication needs in low-resource settings. Palliative radiotherapy is a cost-effective intervention to reduce vaginal discharge, bleeding, pressure effects and nociceptive or neuropathic pain caused by pelvic and para-aortic disease. The role of palliative radiotherapy in patients with malignant fistulae is discussed and the literature on hypo-fractionated pelvic radiotherapy is briefly reviewed.

Key words Cancer pain - cervical cancer - foul smell - hypo-fractionated radiotherapy - palliative - rectal obstruction - uraemia

India has the largest number of cervical cancer deaths in the world; globally over 300,000 women die of the disease every year¹. These can be difficult and painful deaths as the tumour infiltrates nerves, ligaments and bones, obstructs lymphatics and vessels, creates recto-vaginal and vesico-vaginal fistulae and produces malodorous discharge^{2,3}. Incontinence and malodour can lead to social isolation, broken marriages, depression and guilt^{4,5}.

Less than one per cent of India's population has access to palliative care⁶. Opioid availability remains a

major constraint even though India is a leading producer of morphine⁶. Small hospitals and non-governmental organizations struggle to obtain oral morphine and to recruit trained staff⁶. India's use of morphine for pain relief is less than one per cent of that in Western Europe and less than 10 per cent of that in South America or South Africa⁷.

In most regions of the country, with the notable exception of Kerala, palliative care services are few and far between⁶. Since exhausted family caregivers may not be able to travel from one hospital to another to

access palliative care, patients can die in excruciating pain. Hence it becomes imperative that pain relief and palliative care are integrated within cancer hospitals, while striving for broader coverage at the community level.

Since cancer specialists understand the clinical course and complications of the disease, they can be equipped with skills to provide palliative care. Palliative care training can be obtained through short-term placements and online educational resources. Such training for oncologists offers several benefits: (i) patients get pain relief and supportive care alongside oncologic treatment ensuring integration and continuity of care; (ii) good communication and early symptom control can improve compliance and cure rates for early stage disease; (iii) futile interventions can be reduced, and healthcare resources can be deployed more effectively; (iv) trainees acquire skills in caring for patients at all stages of cancer and are therefore less likely to feel inadequate when they move on to practice in smaller settings; (v) site-specialized oncologists can research and develop site-appropriate palliative care protocols.

Some online links to important training resources and directories of palliative care services within India are provided in Supplementary Annexure I.

Even in busy low-resource settings, it is possible to improve quality of life by using palliative care principles and palliative radiotherapy⁸⁻¹⁰. The patient's personal goals and quality of life should take precedence over treatment protocols when the cancer is incurable. The ethical framework of beneficence and non-maleficence (benefits vs. burdens), justice (the fair and equitable use of limited resources) and patient autonomy enables patient-centred decision-making in complex situations¹¹. Analgesic subsidy and caregiver education are essential to ensure that impoverished and vulnerable women receive the medicines that are prescribed¹².

A hypothetical clinical scenario in Supplementary Annexure II (available online) illustrates practical aspects of symptom control, interdisciplinary care, communication and clinical decision-making in a patient with recurrent cervical cancer.

Uraemia in advanced cervical cancer

Ureteral obstruction from cervical cancer occurs most often in the Mackenrodt's ligaments, proximal to the vesico-ureteric junction. In advanced cervical

cancer, it may be caused by enlarged metastatic lymph node(s) in the common iliac or para-aortic regions or a direct tumour extension, resulting in encasement of the ureter¹³. Post-treatment fibrosis can also entrap the ureters and cause hydronephrosis in patients without recurrent disease. Hydronephrosis due to ureteral obstruction by cancer, particularly if bilateral, may result in varying degrees of renal insufficiency¹³. Uraemic symptoms include anorexia, lethargy, pruritus, nausea, vomiting, breathlessness, seizures, delirium and coma. A recent systematic review concluded that hydronephrosis is associated with poorer survival rates in cervical cancer with hazard ratios for overall survival ranging between 1.34 and 3.74¹⁴.

Options for decompression of the obstructed ureters include placement of ureteral stents or percutaneous nephrostomy (PCN). While PCNs are more frequently used because of technical feasibility, these are not short of complications such as urinary leakage, excoriation at the nephrostomy exit site and kinking of tubes¹⁴. In a retrospective analysis of 50 consecutive patients with recurrent cervical cancer who underwent PCN, 44 per cent had intervention-related morbidity. Urinary infections occurred in 20 per cent and catheter dislodgement of the catheter in 18 per cent. Although renal parameters improved in 60 per cent of cases, only 14 per cent had an improvement in performance status and 22 per cent of patients could not be discharged from the hospital. The median survival was 8.9 wk¹⁵.

Even in a well-resourced Scandinavian country, patients with PCNs struggled with discomfort, stigma, limitation of activities, recurrent emergency room visits and complexity of dressings¹⁶. Analysing a cohort of 270 patients, Aravantinos *et al*¹⁷ observed that although the procedure was relatively simple and their complication rates were low, there was no improvement in the quality of life of the patients with obstructive uropathy due to advanced gynaecological cancers.

In summary, PCN, often seen as an emergency 'life-saving option' by the physician and patient, should be undertaken only after prognosis, benefits and burdens have been carefully considered and clearly communicated to the patient as well as the caregivers. It should be recommended mainly in cases when curative treatment options are expected to be beneficial.

In cases of incurable locally recurrent cervical cancer, a PCN can relieve obstructive uropathy; however, as the disease progresses, the patient

may develop fistulae or rectal obstruction. These complications are not immediately life-threatening but can cause great suffering¹⁵. There may be patients who have important legal or social reasons for wishing to prolong life even for a few weeks. The physician needs to communicate prognosis and outcomes with honesty and sensitivity. Patients and families will have fewer regrets if they have made an informed choice after having understood the limited role of urinary diversion and the likely course and complications of the illness¹⁵.

Palliative radiotherapy in cervical cancer

Palliative radiotherapy can help provide more sustained symptom control, reduce analgesic requirement and improve quality of life¹⁸. Kim *et al*¹⁹ and van Lonkhuijzen *et al*¹⁸ have summarized the results of single-arm studies of palliative radiotherapy. Hypofractionated radiotherapy, 8-10 Gy given for 1-3 fractions, helped control bleeding in 45 and 100 per cent, pain in 0 and 100 per cent and vaginal discharge in 39 and 49 per cent of patients²⁰⁻²⁴. Severe late toxicities ranged from 8-12 per cent^{18,19}. This is likely to be an underestimate¹⁸ as several of these were retrospective studies with incomplete follow up.

The prospective study, RTOG 7905, was terminated early because of severe late gastrointestinal toxicity in patients who received 10 Gy \times 3 fractions, along with the radiosensitizer misonidazole²⁵. Subsequently, RTOG 8502 used twice daily radiotherapy, 3.7 Gy BD \times 2 days, 14.8 Gy per cycle, repeated every month for up to three months and observed lower actuarial rates for severe late toxicity (6.9% vs. 49%) as compared to RTOG 7905^{24,26}. Short courses of conformal radiotherapy – 5 Gy \times 5 fractions, 4.5 Gy BD \times 4 fractions have been used more recently^{19,27}.

Most women living in resource-limited countries with incurable cervical cancer do not have access to palliative care. Safe and simple palliative radiotherapy regimens need to be defined through randomized trials¹⁸. Such evidence is lacking in gynaecological cancers. However, in a multicentre randomized trial in patients with advanced bladder cancer, palliative pelvic radiotherapy at 7 Gy per fraction for three fractions was as good as 35 Gy in 10 fractions, with respect to symptom improvement and acute toxicity²⁸.

Short course hypofractionated treatments of 1-3 fractions should be offered only to carefully selected patients with a limited life expectancy who are not likely to live long enough to develop severe late radiation toxicity²⁹. Prudently used in such patients,

hypofractionated radiotherapy provides early symptom relief and reduces hospital visits.

Radiotherapy in metastatic para-aortic and supraclavicular lymphadenopathy: Patients with advanced/recurrent cervical cancer may also present with difficult extra-pelvic symptoms caused by metastatic nodes. Para-aortic nodes can cause refractory nociceptive and neuropathic pain due to the infiltration of bone, retroperitoneal soft tissues or nerve roots. Such pain is often inadequately controlled with analgesics. Palliative radiotherapy should be considered to provide sustained pain relief and prevent further nerve damage³⁰.

Palliative radiotherapy in patients with fistula: Management of complicated fistulas in patients with local pelvic malignancies can be challenging, especially when associated with local disease. Recto-vaginal and vesico-vaginal fistulae are not uncommon in women with advanced cervical cancer. Surgical diversion provides only partial palliation as patients continue to experience cancer-related pain, bleeding and vaginal discharge. Pelvic radiation is often not considered in these patients for fear of worsening the fistula. Although the evidence for the use of radiotherapy in such situations is sparse, palliative radiotherapy can be incorporated in patients with the intention of improving outcomes³¹.

Radiotherapy planning: Treatment portals for pelvic radiation include conventional parallel-opposed anterior-posterior fields delivered with a tele-cobalt unit or a linear accelerator. Alternatively, conformal radiotherapy can be used for a more homogenous dose distribution and relative bowel sparing. The choice of field sizes and target volumes should be individualized depending upon the life expectancy, performance status, comorbidities, history of previous irradiation at the site of recurrence, treatment goals and institutional logistics³².

Other important interventions

While physical symptoms might present as the most urgent problems, but as illustrated in the case study, they are rarely the most important long-term concerns for the patient or the family. Social workers, volunteers and non-governmental organizations can help with food and drug subsidy, children's education, income-generation, family counselling and home care³³. A directory of such resources should be available in every cancer clinic. These important, but often forgotten; practical measures may have a

lasting impact on the survival and the sustenance of the bereaved family.

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For correspondence: Dr Bhavana Rai, Department of Radiotherapy & Oncology, Regional Cancer Centre, Postgraduate Institute of Medical Education & Research, Chandigarh 160 012, India
e-mail: bhavana1035@gmail.com

Supplementary Annexure I. Links to directories of palliative care services and resources for palliative care training within India

<https://ecancer.org/en/elearning/course/16-palliative-care-e-learning-course-for-healthcare-professionals-in-india>: Online modules

<https://www.palliativecare.in/>: Directory of services

<https://palliumindia.org/training/training-calender>: Directory of services, online and onsite training programmes

<https://www.palliativecare.in/iapc-academy-online-training-program-series-2-lecture-11/>: Online training series

<https://www.instituteofpalliativemedicine.org/courses.php>: Online and onsite training programmes

<https://ncgeducation.in/>: Online courses

<https://cansupport.org/palliative-care-training/>: Online and onsite training programmes

Supplementary Annexure II. Palliative care for recurrent cervical cancer: An example

First visit to the integrated cancer palliative care clinic

A 45 yr old† woman who has completed radical chemo-radiotherapy for carcinoma cervix is detected to have a local recurrence and is advised palliative care.

History

- (i) The nurse/social worker/trained volunteer documents a family tree, psychosocial history and a symptom checklist.
- (ii) The doctor reviews clinical notes, asks the patient to describe how the problem evolved, listens without interruption and then asks questions to clarify anything else he needs to know.

Physical symptoms

Severe pain in the gluteal region and radiating down the left lower limb; insomnia & foul smelling vaginal discharge

Information needs

- (i) The patient thinks that new medicines to cure the disease will be started but further radiotherapy and surgery are not planned.
- (ii) The husband knows that the disease is incurable. He has told the nurse that the smell is unbearable. Relatives have been telling him to send his wife away to prevent the 'infection' from spreading to others.

Economic concerns

The patient and her husband are worried that the money they have borrowed for their daughter's forthcoming marriage will be used up for further treatment.

Psychosocial and spiritual concerns

The patient feels guilty, unclean and isolated because of the smell. She is scared that her husband will leave her. A neighbour has told her that cancer is a punishment from God.

Physical examination

The patient's performance status is ECOG 2. She has no supraclavicular nodes, pedal oedema or clinical features, suggestive of systemic disease. On pelvic examination, there is necrotic tumour infiltrating all fornices and the upper vagina. Both parametria are infiltrated up to the lateral pelvic wall. The utero-sacral ligaments and the recto-vaginal septum are infiltrated, but there is no fistula. The rectal lumen is rigid and about 1.5 cm in diameter. Profuse smelly discharge is present.

Summary

Post-radiotherapy inoperable local recurrence of cervical cancer, with rectal narrowing, a normal creatinine, poor socio-economic status and fragile family support and a likely prognosis of several months.

Initial management

- (i) Since this is his first meeting with the patient, the doctor decides to alleviate physical symptoms, establish trust and discuss the prognosis after pain is better.
- (ii) He explains to the patient's husband that the disease is not contagious and that the smell can be controlled. He appreciates the husband for having taken good care of the patient through her anti-cancer treatment and requests him to continue supporting her in her final months.
- (iii) After confirming that the recent serum creatinine is within normal limits, the doctor prescribes the following:
 - (a) For severe nociceptive cancer pain, Step 3 of the WHO analgesic ladder^{1,2}
 - Tablet morphine 5 mg q4h and s.o.s. for breakthrough pain (strong opioid)
 - Tablet paracetamol 1 g at night and s.o.s. (non-opioid)
 - (b) For neuropathic pain, insomnia and low mood³
 - Tablet mirtazapine 3.75 mg at night
 - (c) To prevent opioid-induced constipation and nausea
 - Tablet bisacodyl 10 mg at night
 - Tablet domperidone 10 mg t.i.d for three days and then s.o.s
 - (d) To reduce smell, he prescribes metronidazole according to the SNIFFF ladder^{4,6}
 - Tablet metronidazole 400 mg t.i.d. for seven days followed by
 - Tablet metronidazole 200 mg once daily to continue

The doctor assures the patient the pain will be better and that the medicines will not be expensive. After the patient collects the medicines, the nurse educates them about nursing measures such as perineal care and about the safe storage and correct administration of medications.

Contd...

Second visit to the integrated cancer palliative care clinic

Reassessment and breaking bad news

The nurse or social worker or counsellor or trained volunteer reviews the serious psychosocial concerns noted on the previous visit and documents any important changes.

The doctor reviews the patient

Pain has reduced by 75 per cent. There were two episodes of breakthrough pain, which settled within an hour of taking an extra dose of oral morphine.

- Tablet morphine is continued at the same regular and s.o.s. dose.

Sleep is still disturbed by burning pain in the left lower limb

- Tablet mirtazapine is increased to 7.5 mg at night.

The patient says that although she has daily bowel movements, stools are hard

- Syrup cremaffin 10 ml is added at night.

The smell is well controlled and vaginal discharge has reduced

- Tablet metronidazole 200 mg once daily is continued.
- If the smell worsens, she is asked to take another course of tablet metronidazole 400 mg three times a day for one week.

The social worker has noted that husband is more supportive. The patient tells the doctor that she is confident that cancer will be cured. The doctor asks her if she would like to know the details of her disease status.

Using the six-step SPIKES protocol for breaking bad news, the doctor clarifies the prognosis⁷. He explains that although the patient has received appropriate anti-cancer treatment, the disease has recurred and cannot be cured. The goal of further treatment is to keep her comfortable.

Two months after the first visit to integrated cancer palliative care

Rectal infiltration

- The patient gives a history of passing stools 4-5 times a day and asks if she should stop laxatives. Knowing that disease is compressing the rectum, the doctor suspects increased stool frequency could be due to a spurious, rather than laxative-induced diarrhoea. He asks for a history of tenesmus or incomplete evacuation. His clinical suspicion is confirmed on pelvic examination - the rectum is less than 1cm in diameter and non-pliable. He notes that there is no recto-vaginal fistula.
- The doctor draws a diagram and explains to the patient why she needs a diversion colostomy. The patient is unwilling for the surgery since her daughter is getting married the next week and 'anyway the disease is incurable'.
- Although the benefits of the colostomy would likely outweigh the burdens, respecting patient autonomy, the doctor defers the colostomy. He explains the symptoms of progressive rectal obstruction and asks the patient to return as soon as possible.
 - Cremaffin is increased to 15 ml t.i.d. to prevent impaction.
- The husband reports that the smell has increased again. A breakthrough course of metronidazole is prescribed
 - Tablet metronidazole 400 mg t.i.d for seven days and 200 mg o.d. to continue.

Another month later

Rectal obstruction

- The patient presents with obstipation, colicky pain and a recto-vaginal fistula. The serum creatinine is 1.0 mg/dl, serum albumin is 3.5 g/dl and the haemoglobin is 8.5 g.
- Estimating that the survival could be several weeks or more, the doctors explains that a colostomy would be the best option to avoid unbearable symptoms in the terminal phase. The patient undergoes a diversion colostomy and has relief from colicky pain and faecal incontinence.
- Medicines for cancer-related nociceptive and neuropathic pain are continued
 - Tablet morphine 10 mg q4h and if needed for breakthrough pain.
 - Tablet mirtazapine 7.5 mg at night.
 - Tablet metronidazole 200 mg o.d. to continue.
 - Tablet bisacodyl 5-10 mg at night to be omitted on days when stools are loose.

Five months after the first visit to the oncology-palliative care clinic

Obstructive uropathy and uraemia

Contd...

- (i) The husband reports that the patient has been bed-bound since two weeks. She is nauseous, has occasional hiccups and is passing very little urine. Tests done at a local hospital show a serum creatinine of 5.0 mg/dl. The hospital has advised bilateral PCN 'to prevent kidney failure'. The patient has been refusing tubes and hospital visits. The husband is very worried. He asks the doctor if he should mortgage his house to finance further treatment.
- (ii) The doctor clarifies that the procedure would not cure the patient and explains the clinical course with or without a PCN. Although the creatinine might improve, recurrent cancer would continue to progress. PCN leakage, displacement, discomfort and infections could lead to repeated hospital visits.
- (iii) The doctor senses that the husband is worried that he not doing the best for the patient. The doctor explains that when the disease is incurable, it would be best to respect the patient's wishes and to focus on dignity and symptom control rather than on laboratory reports or procedures of limited benefit.
- (iv) Since the creatinine is high and pain is less severe, the medications are titrated down
 - Stop regular oral morphine and mirtazapine.
 - Tablet paracetamol 500 mg t.i.d. and s.o.s.
 - If pain increases, to add buprenorphine patch 5 µg weekly.
 - Tablet haloperidol 0.5 mg h.s. and if needed for nausea, hiccups or delirium.
 - Tablet metronidazole 200 mg o.d. for malodor.

Six months

Death

- (i) The husband comes to inform that the patient had died a week ago. She had become increasingly sleepy but was pain free and comfortable. She had not required additional pain medications.
- (ii) The husband is grateful that the patient was able to stay at home without pain or smell in her final days and that he was advised not to mortgage his house.

PCN, percutaneous nephrostomy; ECOG, Eastern Cooperative Oncology Group

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