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**Review Article**

# Defining the role of high-dose radiation in oligometastatic & oligorecurrent cervical cancer

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**Around 5-8 per cent of women diagnosed with cervical cancer present with metastatic disease at presentation and 16-25 per cent of patients fail at either within irradiated fields or at distant sites post-curative therapy in advanced cervical cancers. Conventionally, chemotherapy with palliative intent constituted the mainstay of treatment with modest survival outcomes and radiation therapy was reserved for symptomatic benefit only. While targeted therapies and immunotherapy have been added in therapeutic armamentarium, the impact on the outcomes is modest. In limited metastatic disease, radiation therapy to metastatic sites from different primary cancers has shown survival benefits; however, the data are scarce in cervical cancer. With a better understanding of the molecular biology of the metastases and recurrence pattern, emphasis is laid upon total eradication of the disease rather than offering relief from symptoms. This article summarizes the role of radiation therapy in limited metastatic disease and recurrent cervical cancer.**

**Key words** Cervical cancer - curative therapy - immunotherapy - metastatic - oligometastatic disease - radiation therapy - recurrent - SBRT

Cancer of the cervix is one of the most frequently diagnosed cancers among women. Every year, 575,000 women are diagnosed with invasive cervical cancer globally, with 13,800 in the United States, 54,500 in Europe and 96,922 in India with 65-75 per cent presenting in locally advanced stage[1,2]. The incidence of metastatic disease at the time of diagnosis ranges from five to eight per cent[2–4]. The 10 yr actuarial incidence of distant metastases ranges from 26, 39 and 75 per cent in International Federation of Gynaecology and Obstetrics (FIGO) stage IIB, IIIB and IVA, respectively[5,6]. Further, the most frequent sites of distant metastases are lung (21-39.3%), para-aortic lymph nodes (PALN) (11%), bone (16.3%), liver (12.2%), abdominal cavity (8%), brain (1.4%) and supraclavicular node (SCLN) (7%)[7,8]. Patients treated with concurrent chemoradiation (CCRT) and brachytherapy (BT) constitute a vast majority of patients who develop disease relapse at distant sites. The disease-free survival (DFS) in FIGO stage IIB-IV is 61-76 per cent, suggesting that close to 25-35 per cent of patients will present with

progression[9]. Post-treatment failure is observed at distant sites in 16-25 per cent of patients[10–13].

Chemotherapy (CTh) administered with palliative intent constitutes the mainstay of treatment in metastatic or recurrent setting with dismal survival of 2-18 months[14–21]. Recently, metastatic disease or recurrent disease has been classified based on number of lesions, sites of involvement; with limited number (usually <3) and involvement as oligometastatic disease (OMD)[22]. Niibe and Hayakawa[23] have suggested that if OMD is eliminated, a patient may be cured, as occurs in loco-regional tumours. A phase II trial by Palma *et al*[24] utilizing stereotactic body radiation therapy (SBRT) in addition to systemic CTh in OMD reported overall survival (OS) benefit in the SBRT arm with grade 2 or higher toxicity 29 per cent with 4.5 per cent mortality in the SBRT arm versus nine per cent and no mortality in the standard of care arm. In addition, the updated analysis has shown durable response and no detrimental effect on the quality of life (QOL) of the patients[25]. Although the study had multiple primary cancer subtypes with OMDs, only a limited number of patients had gynaecological cancer and no patients with cervical cancer were included.

An international coordinated effort (ESTRO-ASTRO consensus) is in the process to better define this patient population that may benefit from intensified treatment approaches[26]. OMD presently includes patients who present with ≤3 metastasis and >3-5 metastases which is largely independent of the primary tumour and metastases location[26]. ESTRO-EORTC group has further classified OMD considering the timing of presentation of metastases, receipt of any systemic therapy before appearance of lesion and response of metastases to the systemic therapy[22].

This review summarizes the existing evidence for the use of RT in the treatment of OMD and ORD in cervical cancer.

## Role of systemic therapy agents

Currently, the recommended standard first-line regimen for the treatment of metastatic cervical cancer is the combination of cisplatin and paclitaxel, which has shown mild to modest improvement[18]. In addition, other chemotherapeutic agents including topotecan[15,19] and gemcitabine[17] have been investigated and have shown slight improvement. Further, addition of immunotherapy and targeted therapies such as bevacizumab, pembrolizumab and cediranib has shown promising results, with bevacizumab combined with standard CTh recommended as a first-line therapy in metastatic or recurrent cervical cancer[16,20,27].

Though the results of these therapies are encouraging, their cost, availability and storage in developing countries have been a challenge and a limiting step for access. A cost-effective analysis done by Klag *et al*[28] suggested that the combination of cisplatin and paclitaxel was the most cost-effective regimen and the addition of bevacizumab, although providing survival benefit, was not sustainable. Phippen *et al*[29] suggested that the addition of bevacizumab to CTh was not affordable.

## Combining radiation with targeted agents and immunotherapy

Various trials are underway combining SBRT or hypofractionated high-dose RT therapy and immunotherapy (NCT03452332, NCT03277482, NCT03614949, NCT03312114, NCT03192059) in recurrent or metastatic cervical cancer as shown in Table I. The accrual of these trials is ongoing, and the results are awaited which will help to further define the management and the optimal dose and fractionation schedules of RT.

## Role of pelvic radiation in patients with *de novo* metastatic disease

In patients with limited metastatic disease at the time of first clinical presentation, integration of local therapy with systemic therapy has been used by various investigators which has shown to provide progression-free survival (PFS) and OS benefits. The primary goal of delivering local therapies is to eradicate the local disease which could translate into clinical and survival benefits. Stenger *et al*[30] analyzed 3169 patients of upfront metastatic cervical cancer treated with CTh alone versus CTh and pelvic RT; the addition of pelvic RT demonstrated significant survival benefit (23.2 *vs.* 10.1 months). Further, the median survival was longer in patients receiving RT dose >45 Gy and those receiving brachytherapy along with external beam RT with benefit seen even in patients with distant and nodal metastasis. A retrospective analysis of 2838 patients confirmed survival benefit (19.2 months vs. 10.1 months) with local definitive RT with CTh as compared to systemic CTh and palliative RT[31]. Another retrospective analysis by Yin *et al*[32] confirmed the benefit of definitive RT with CTh over palliative RT and CTh and observed that mortality was due to distant progression rather

**Table I.** Ongoing clinical trials of radiotherapy and immunotherapy in cervical cancer

| Clinical trial identifier | Diseases | Immunotherapy | Radiation therapy | Endpoint | Secondary endpoint |
|---|---|---|---|---|---|
| NCT03452332 Phase I | Recurrent or metastatic cervical, vaginal or vulvar cancers | Tremelimumab + durvalumab | SABR with 3 fractions separated by 48 h | AE | Response to treatment; PFS; OS; TTNT |
| NCT03277482 Phase I | Metastatic or unresectable endometrial, ovarian (ovarian epithelial, fallopian tube, primary peritoneal), cervical, vaginal or vulvar cancer | Tremelimumab and durvalumab | Hypofractionated short course (either 1 or 5 days) | MTD | ORR; LRR, LCR, ARR, RD; PFS, OS |
| NCT03614949 Phase II | Recurrent or metastatic cervical cancer | Atezolizumab q3w 1 week | SBRT with 24 Gy in 3 fractions | ORR | PFS; OS |
| NCT03312114 Phase II | Metastatic fallopian tube cancer, primary peritoneal carcinoma, recurrent epithelial cancer of ovary | Avelumab | Stereotactic treatment (*e.g.* SABR/SBRT) | ORR | OS; CR; TTP; median response duration |
| NCT03192059 Phase II | Advanced or refractory cervical cancer, endometrial carcinoma, or uterine sarcoma | Immunomodulators Vitamin D, aspirin, cyclophosphamide, and lansoprazole plus curcumin with pembrolizumab | EBRT 24 Gy in 3 fractions, a fraction every 28 h | ORR | Incidence of AE; best OR; PFS; OS |

AE, adverse event; ARR, abscopal response rate; CR, complete response; LCR, local control rate; LRR, local-regional recurrence; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RD, response duration; SABR, stereotactic ablative radiation therapy; SBRT, stereotactic body radiation therapy; TTNT, time to next treatment; TTP, time to progression; EBRT, external beam radiation therapy

than local progression after definitive RT. European Society for Medical Oncology (ESMO), European Society of Gynaecological Oncology (ESGO) and European Society for Radiotherapy and Oncology (ESTRO) guidelines also recommend treating pelvis (gross disease with elective irradiation of immediate nodal level) with CTh in localized metastatic disease[33]. Local RT also helps to alleviate the symptoms and pain associated with the disease. In a survey conducted within the EMBRACE group, it was revealed that all the participants agreed on delivering local RT in OMD with 68.2 per cent preferring CCRT and BT while 31.8 per cent preferred adding systemic therapy[34]. There is evidence that local RT improves survival in metastatic cervical cancer at presentation as shown in above studies; though most of the data are retrospective and prospective studies are needed. Further, no robust evidence exists about the benefit of elective irradiation of nodal targets while delivering local RT in such settings.

## Role of radiation therapy in patients with metastasis to distant nodal sites

The spread of cervical cancer is stepwise with involvement of pelvic lymph nodes first followed by PALN and then systemic organs[35].

*Supraclavicular nodal (SCLN) metastasis:* The incidence of SCLN metastasis is approximately 1.5-8.6 per cent with or without PALN metastasis at presentation with a five-year OS rate of 16.5 per cent[36,37]. In a study of 24 patients who had distant nodal metastases at presentation, patients receiving CCRT followed by BT had better PFS and OS and complete response (CR) rates as compared to those receiving CTh alone[38]. In a retrospective analysis, 25 patients with both para-aortic nodes (PALN) and SCLN metastases received RT to the PALN and left SCLN (59.4 Gy) and 50.4 Gy to the pelvis with platinum-based CTh concurrently followed by BT. The median OS of the patients was 32 months

with 64 per cent experiencing grade 3 or more acute haematologic toxicity[39]. Another study done in seven patients reported five year OS of 57 per cent when RT was delivered to SCLN along with pelvic RT and CTh, although the rate of acute haematologic toxicity was 67 per cent with no chronic toxicities[40]. In another study of 38 patients treated with definitive RT to OMD sites of cervical cancer including SCLN, mediastinum, lung and PALN, the median OS was 50.7 months and PFS was 21.7 months with <3 per cent grade ≥3 toxicity[41]. In such patients, CCRT followed by CTh was feasible with acceptable late toxicity, although the acute haematologic toxicity was reported to be higher. However, given uncommon presentation and differences concerning treatment, no consensus exists about the RT dose to SCLN. In addition, whether the target volume should include the entire nodal chain or only the involved node is unclear, and more studies focussing on these aspects are needed.

*Inguinal nodal metastasis*: The incidence of inguinal nodal metastasis at diagnosis is <2 per cent[42]. There are no robust guidelines for the management of inguinal node metastases; most of the evidence is based on case reports and individual practices. Being close to pelvic RT fields, the majority of RT oncologists extend the RT fields to include the inguinal nodes with concurrent CTh, with RT doses up to 45 Gy to the pelvis with an additional 9-15 Gy boost are recommended for the involved inguinal nodes and the preferred CTh agent is cisplatin 40 mg/m$^2$ weekly[43]. The role of neoadjuvant or adjuvant CTh or node dissection is not defined in such a setting.

*Mediastinal nodes metastasis*: The incidence of mediastinal nodes at diagnosis is rare and is under-reported. Positron emission tomography computed tomography (PET-CT) is useful in the diagnosis of mediastinal nodes along with thoracotomy or video-assisted thoracic surgery. SBRT is becoming an attractive modality of treatment in recent times and a retrospective analysis of 52 patients with 84 mediastinal and hilar nodes treated with SBRT median dose of 35 Gy (range 30-50) in five fractions improved OS to 31.7 months[44]. A total of nine per cent local failures were observed at two years and 11.5 per cent of patients experienced grade 3 or more toxicity; however, a vast majority of toxicities were transient with 1.9 per cent developing grade 5 toxicity (radiation pneumonitis). The authors concluded that SBRT to mediastinal and hilar lymph node metastases was feasible with acceptable toxicity.

### *Cervical cancer with visceral metastases*

Cervical cancer with lung metastasis: Approximately 4.1-7.7 per cent of patients with cervical cancer develop lung metastasis[7,45]. The number of nodules, possibility of surgical resection (SR), time interval between the appearance of metastases and initial treatment and receipt of CTh affect the outcomes[46,47].

In selected patients who present with limited metastatic disease, SR or RT targeting metastatic sites with systemic therapy should be offered. In a retrospective review of 529 patients with 776 lesions, after lung metastasectomy, the ninety month survival rate was 30 per cent, however very few patients with good general condition and adequate pulmonary reserve could undergo surgery[48]. SBRT is a feasible approach to resection. There are limited studies on SBRT in pulmonary oligometastatic setting, and most of the evidence of SBRT in the lung was derived from stage I non-small cell lung cancer who were medically inoperable[49,50]. Studies utilizing SBRT in lung metastases from various primary cancers in *de novo* metastatic or recurrent setting are shown in Table II. In dose-escalation studies, patients treated with 8 Gy ×5 fractions showed CR in 51 per cent and partial response in 33 per cent with only one patient experiencing grade 3 or more toxicity[60]. In another dose-escalation study, SBRT was delivered 20 Gy ×3 fractions in 38 patients with 63 lesions, the actuarial local control (LC) was 96 per cent at two years with a median OS of 19 months with only eight per cent experiencing grade 3 or more toxicity[61]. Hou *et al*[62] treated 19 patients with cervical cancer with 29 lung metastases with 56-64 Gy in 7-8 fractions and the one-year LC and OS were 75.6 and 76.8 per cent with only one patient developing grade 3 pneumonitis. They concluded that SBRT was safe and efficacious and could be an alternative to surgery[62]. Patients with a good general condition, limited pulmonary metastases (three or fewer), adequate pulmonary function and potentially treatable extra-thoracic disease can be considered as suitable candidates for SBRT. Total dose, fractionation depends upon the location of the tumour and proximity to critical structures. Based on two studies[63,64], dose constraints for SBRT in lung primaries are shown in Table III.

Cervical cancer with liver metastases: The incidence of cervical cancer with liver metastases is 1.2-2.2 per cent, with poor survival with CTh alone[65]. In limited liver metastases, resection of metastases is traditionally the choice of treatment with the majority of evidence

**Table II.** Studies evaluating the role of stereotactic body radiation therapy in lung metastasis

| Study | Number of patients | Number of lung lesions | Primary site | Dose | LC | Toxicity |
|---|---|---|---|---|---|---|
| Wulf *et al*[51], 2004 | 41 | 51 | All (majority lung) | 26-30 Gy SF<br>30-36 Gy/3# | One year LC 80 per cent | Grade 2 pnemominits 3 per cent |
| Hof *et al*[52], 2007 | 61 | 71 | All (majority lung) | 24-26 Gy SF | Two years PFS 73 per cent | G3 pnemonitis 5 per cent |
| Ricardi *et al*[53], 2012 | 61 | 77 | All (majority lung) | 26 Gy SF<br>45 Gy/3# | Two years LC 89 per cent | G3 pneumonitis 1.6 per cent |
| Osti *et al*[54], 2013 | 66 | 103 | All (majority lung, rectal, breast) | 22 Gy (central)<br>30 Gy (peripheral) | Two years LC 82 per cent | G3 pneumonitis 11.9 per cent |
| Filippi *et al*[55], 2014 | 67 | 90 | All | 26 Gy | Two years LC 88 per cent | G3 pneumonitis 1.6 per cent<br>Chest wall toxicity-8.9 per cent |
| Wersäll *et al*[56], 2005 | 58 | 117 | RCC | 30-40 Gy/3#/1 week | LC 90 per cent at median FU 37 months | |
| Milano *et al*[57], 2012 | 121 | 103 | All (majority breast and CRC) | 50 Gy/10# over 2 weeks | Two years LC 77 per cent | G3 lung in 1 patient |
| Kang *et al*[58], 2010 | 59 | 18 | All (majority CRC) | 39-51 Gy/3# | Three years LC 66 per cent | G1-2 pneumonitis in 46 per cent |
| Salama *et al*[59], 2011 | 61 | 41 | All | 24-48 Gy/3# | Two years LC in 66 per cent | G3 pneumonitis in 1 patient |

LC, local control; CRC, colorectal cancer; RCC, renal cell carcinoma; Gy, gray; SF, single fraction, #: fractions

comes from colorectal cancer and has shown excellent outcomes[66–74] as shown in Table IV. LC of liver metastases by use of SBRT is promising, providing 60-90 per cent at two years; however, tumour volume, receipt of prior CTh and RT dose have a definite role to play[68–71]. In spite of good local LC in treated site, distant progression is the cause of mortality; hence, combining systemic therapy with SBRT is justified; however, the sequencing of these therapies is crucial for adequate tumour control and survival. Severe toxicity related to SBRT is uncommon with the risk of RT-induced liver disease reported in SBRT is low[75].

In a study evaluating the role of SBRT in various OMD sites (lung, liver and nodes) in 45 patients (9 patients with cervix primaries) with 70 lesions, the CR was 64 per cent with no patients progressing after achieving CR at a median follow up of survivors of 40 months with 13 per cent grade 1-2 acute toxicity and no grade 3 or more acute or long-term toxicity; no progression was seen in patients who achieved CR[76]. A similar study of treating oligometastatic sites with definitive RT has shown improved survival 42 (95% confidence interval: 21-63) months with no local or in-field recurrence[77]. Studies using high dose per fractions schedule with the aim to deliver ablative doses have shown improved survival in OMD at presentation[78-80] and including recurrent disease post-curative therapy as well[81,82]. Administration of CTh before SBRT has shown poor tumour control likely due to the killing of sensitive clones and remains of CTh-resistant clones[83]. This study predicted that in patients receiving no CTh before SBRT, biological effective dose (BED) of 209±67 Gy, but in those receiving CTh prior to SBRT, BED of 286±78 Gy needed for 90 per cent control probability at two years. In addition, BED >100 Gy, tumour volume <40 $cm^3$ and metastasis with the head neck (median 37 months) and breast (32 months) primary tumours have better survival than arising from colorectal (30 months) and lung primaries (26 months)[84]. In a study by Hong *et al*[85] in 89 patients treated with SBRT to liver metastases,

**Table III.** The recommended dose volume constraints for stereotactic body radiation therapy in early stage non-small cell lung cancer

| Parameters | RTOG 0236 protocol[63] | RTOG 0915 protocol[64] | |
|---|---|---|---|
| Dose prescription | 60 Gy/3# | 34 Gy/1# | 48 Gy/4# |
| PTV | 95 per cent PD to 95 per cent volume<br>99 per cent PD to 90 per cent volume | 95 per cent PD to 95 per cent volume<br>99 per cent PD to 90 per cent volume | 95 per cent PD to 95 per cent volume<br>99 per cent PD to 90 per cent volume |
| CTV | 100 per cent PD to 100 per cent volume | 100 per cent PD to 100 per cent volume | 100 per cent PD to 100 per cent volume |
| Spinal cord | Max <18 Gy | Max <14 Gy <0.35 $cm^3$-10 Gy <1.2 $cm^3$-7 Gy | Max 26 Gy <0.35 $cm^3$-20.8 Gy <1.2 $cm^3$-13.6 Gy |
| Lungs | V20 <10-15 per cent | <1500 $cm^3$-7 Gy <1000 $cm^3$-7.4 Gy | <1500 $cm^3$-11.6 Gy <1000 $cm^3$-12.4 Gy3 |
| Heart | Max <30 Gy | Max <22 Gy<br>15 $cm^3$ <16 Gy | Max <34 Gy <15 $cm^3$-28 Gy |
| Oesophagus | Max <27 Gy | Max <15.4 Gy<br>5 $cm^3$<11.9 Gy | Max <30 Gy |
| Proximal bronchial tree | Max <30 Gy | Max <20.2 Gy<br>4 $cm^3$ <10.5 Gy | Max <34.8 Gy <4 $cm^3$-15.6 Gy |
| Skin | Max <24 Gy<br>10 $cm^3$ <40 Gy | Max <26 Gy<br>10 $cm^3$ <23 Gy | Max <36 Gy <10 $cm^3$-33.2 Gy |
| Brachial plexus | Max <24 Gy | Max <17.5 Gy<br>3 $cm^3$ <14 Gy | Max <27.2 Gy <3 $cm^3$-23.6 Gy |

Superscript numerals denote reference numbers. PD, prescription dose; Gy, gray; PTV, planning target volume; CTV, clinical target volume; RTOG, Radiation Therapy Oncology Group

the mutation in *KRAS* oncogene was the strongest predictor of poor LC and tumours with both *KRAS* and *p53* mutation were radioresistant with one-year LC 20 per cent versus 69.2 per cent in the non-mutated cohort. This study highlights the importance of tumour genotyping before SBRT and treatment intensification in such a subset of patients[85]. Ideal candidates for liver metastasis SBRT should have a good performance status, sufficient hepatic reserve, no metastatic disease outside liver and an uninvolved liver volume of 700 ml or greater. Table V shows dose constraints from different studies for liver SBRT.

Cervical cancer with bone metastasis: Bone metastases incidence varies from 0.8 to 23 per cent in cervical cancer[87,88]. Vertebral column, mainly the lumbar and thoracic spine (48%) followed by pelvis, is the most common site of involvement, with the majority of them (67%) detected within the first year of the radical treatment. Vertebral metastases, if left untreated or delayed, can cause spinal cord compression and irreversible neurological deficit. RT can provide pain relief and can stabilize fractures; however, the majority of patients can relapse[87]. In a study of 105 patients treated with an RT dose of 30 Gy in 10 fractions, the median survival was 10 months with 60 per cent of patients responding to pain. In addition, the use of local treatment was associated with improved survival than the survival of seven months observed in patients receiving CTh alone ($P$=0.011)[89]. In spine metastases, the traditional dose fractionation regimen used was 8 Gy single fraction, 20 Gy in five fractions and 30 Gy in 10 fractions providing good symptomatic relief but poor LC. With high-dose SBRT ranging from 15 to 45 Gy in 1-5 fractions, LC improves along with PFS and delay in CTh switchover[90]. In other histologies, bone SBRT has increased LC up to 85-90 per cent using 15-30 Gy in 1-3 fractions[91,92]. In a retrospective analysis of 1400 patients, LC was 90 per cent at 15 months post-SBRT with <1 per cent risk of myelopathy[93]. In

**Table IV.** Studies evaluating stereotactic body radiation therapy in liver metastases

| Study | Lesions | Patients | Primary | Dose | LC | Survival | Toxicity |
|---|---|---|---|---|---|---|---|
| Blomgren *et al*[69], 1995 | Variable | 31 | Mixed | 8-66 Gy/1-4# | 80 per cent | NR | Haemorrhagic gastritis in 2 patients |
| Hoyer *et al*[70], 2006 | 1-6 cm (<6) | 44 | Majority CRC | 45 Gy/3# | Two years 86 per cent | Two years 62 per cent | Liver failure 1 Gastritis 2 |
| Rusthoven *et al*[67], 2009 | 1-3 (<6 cm) | 47 | Majority CRC | 60 Gy/3# | Two years 92 per cent | Median 17 months | Grade 3 <2 per cent |
| Lee *et al*[71], 2009 | Variable | 68 | Majority CRC | 28-60 Gy/3# | One year 71 per cent | Median 18 months | Grade 3-8 patients Grade 4-1 patients |
| Goodman *et al*[72], 2010 | 1-5 (<5 cm) | 26 | Majority CRC | 18-30 Gy/1# | One year 77 per cent | OS One year 62 per cent Two years 49 per cent | Grade 2-4 patients |
| Rule *et al*[73], 2011 | 1-5 | 27 | Majority CRC | 30 Gy/3# 50-60 Gy/5# | One year 30 Gy 59 per cent 50 Gy 89 per cent 60 Gy 100 per cent | Two years OS 30 Gy 56 per cent 50 Gy 67 per cent 60 Gy 50 per cent | No grade 3 or more tox |
| Mahadeva *et al*[74], 2018 | Variable | 427 | Majority CRC | 45 Gy/3# (range 12-60 Gy) | One year 84 per cent Two years 72 per cent | One year 74 per cent Two years 49 per cent | NR |

Superscript numerals denote reference numbers. CRC, colorectal cancer; Gy, gray; OS, overall survival; LC, local control; NR, not reported; #: fractions

**Table V.** Recommended dose volume constrains for stereotactic body radiation therapy in liver metastases

| Structures | Wulf *et al*[75] | Rusthoven *et al*[67] | Hoyer *et al*[70] | QUANTEC[86] |
|---|---|---|---|---|
| Prescription dose | Low dose group-3×10 Gy or 4×7 Gy prescribed to the PTV-encl 65 per cent isodose High dose group-3×12-12.5 Gy or 1×26 Gy/ PTV enclosing 80 per cent isodose | 12-20 Gy×3 fractions prescribed to isodose line covering PTV | 15 Gy×3 fractions | NA |
| Liver-CTV | 30 per cent <21 Gy 50 per cent <15 Gy | 700 ml <15 Gy | 700 ml <15 Gy | 700 ml <15 Gy Dmean <15 Gy |
| Stomach | D5 ml <21 Gy | Dmax ≤30 Gy | D1 ml <21 Gy | Dmax <30 Gy |
| Bowel | D5 ml <21 Gy | Dmax ≤30 Gy | D1 ml <21 Gy | Dmax<30 Gy |
| Oesophagus | D5 ml <21 Gy | NA | D1 ml <21 Gy | NA |
| Bilateral kidney | NA | Dmax <18 Gy D35 <15 Gy | Dmax <18 Gy D35 <15 Gy | NA |
| Spinal cord | NA | Dmax ≤18 Gy | Dmax ≤18 Gy | Dmax ≤20 Gy |
| Heart | D5 ml <21 Gy | NA | D1 ml <30 Gy | NA |

Gy, gray; PTV, planning target volume; NA, not applicable; CTV, clinical target volume; QUANTEC, quantitative analyses of normal tissue effects in the clinic; Dmax, maximum density

patients post-laminectomy, spine SBRT is feasible with one-year LC ranging from 85 to 95 per cent with no grade three or higher acute or late toxicities[94,95]. In non-spine metastases, SBRT 30-35 Gy in five fractions showed

excellent LC of 87 per cent at two years with 8.5 per cent fracture rates in the treated sites and the man time to fracture was 8.4 months[96]. Similarly, post 24 Gy single fraction, the LC was 91.4 per cent at one year with no late grade three or higher toxicities and pain resolution in 88 per cent of the patients with non-spine bone oligometastasis. Two patients developed pathological fractures, but both were asymptomatic[97]. Various studies[98,99], meta-analysis[100] and ASTRO statement[101] have confirmed that single-fraction RT therapy is as efficacious and safe as fractionated RT; however, the retreatments rates are higher with single-fraction RT. The addition of bisphosphonates and denosumab with RT has shown benefit in reducing skeletal-related events and combining them is prudent. Sprave *et al*[102] assessed QOL in patients with spine metastases post-conventional RT and SBRT, and there was no difference between the two regimens across all domains and pain-related scores.

Cervical cancer with brain metastases: Brain metastasis in cervical cancer is rare ranging from 0.5 to 1.2 per cent[103]. Brain metastases cause not only morbidity and mortality but also neurocognitive decline, leading to poorer QOL. Good prognostic factors are age less than 50 at diagnosis, good performance status, single or less than three lesions and absence of extra-cranial lesions[104].

With palliative whole-brain RT (WBRT), the survival ranges from 3 to 7 months[104,105]. In single or limited metastasis, SR followed by WBRT has shown significantly better outcomes as compared to WBRT alone, 10-11.5 months versus six months[106-108]. Further, the LC rates and OS for patients with a single metastasis treated either with SR followed by WBRT or with stereotactic radiosurgery (SRS) alone are similar[106,107,109,110]. WBRT followed by SR was beneficial to decrease local and distant recurrence, although there was no benefit in OS[111].

SRS plus WBRT has shown benefit in OS (10.6 *vs*. 5.3 months, *P*=0.001), LC (88.9 *vs*. 55.6%) and time to progression (8.1 *vs*. 4 months) as compared to WBRT alone in brain metastasis in lung cancer[113]. Two studies have confirmed that SRS boost has local, survival benefit over WBRT alone in limited brain metastases and should be considered in patients with good performance status and controlled extra-cranial disease[112,113].

Studies evaluating the role of SRS in cervical cancer with brain metastases are limited; however, all three studies have shown survival and LC benefit[114-116].

There is an evidence to suggest that SR when done before WBRT in a single metastasis versus upfront WBRT alone leads to improved OS and functional status in the patients[106,107]. At present, there is no level I evidence justifying WBRT or SRS after surgery and the decision of adjuvant treatment should be made judiciously.

While LC and OS continue to be the prime end points, neurocognitive deterioration should be considered while planning treatment and emphasis must be given to improve the QOL of the patients. The role of SRS is evolving and currently limited to boost after WBRT, as monotherapy in <5 metastases, as salvage therapy after the previous WBRT, post-operative RT and in radio-resistant brain metastases.

Cervical cancer with peritoneal deposits: Peritoneal deposits in squamous cell carcinoma of the cervix at diagnosis are extremely rare and comparatively more in adenocarcinoma than in squamous histology. Conventionally, CTh with palliative intent used to be the treatment modality. One case report has shown that excision of limited deposits followed by CCRT (including the deposit and track site of excision) can be curative and provides long-term disease control and survival. However, no definitive guidelines exist for the treatment of peritoneal deposits and decisions should be made on an individual basis depending upon the patient`s conditions and extent of disease.

de Vin *et al*[117] proposed an algorithm based on four risk factors affecting OS in OMD: presence of non-adenocarcinoma histology, presence of intracranial metastases, synchronous OMD and male gender. Based on this, the OS ranges from 40 to 4 months in the presence of 0 and all four risk factors, respectively[117].

**Locoregional recurrence after curative therapy**

The incidence of nodal recurrence post-curative therapy in locally advanced cervical cancer ranges from 4.7 to 18.9 per cent while the central recurrence (local and regional) rate ranges from 7.6 to 25 per cent and isolated para-aortic ranges from 1.7 to 12 per cent[10,11,13,118,119]. Patients presenting with only local relapse with no distant metastasis can be offered treatments with curative intent with the choice of treatment depending upon the receipt of the prior treatment. Women who are likely to benefit from surgical management include those who present with a central pelvic recurrence without sidewall fixation or associated hydronephrosis, and small tumour size.

Patients who present with loco-regional relapse post-hysterectomy can be offered RT with or without CTh. Vaginal vault or parametrial relapse can be considered for external beam RT with BT or BT alone with five-year survival ranging from six to 55 per cent[120,121]. Mahantshetty *et al*[122] analyzed 30 patients treated with brachytherapy to a median dose of 42 Gy (range 37 to 46 Gy) and reported two-year LC 44 per cent, PFS 42 per cent and OS 52 per cent with grade three proctitis and cystitis and grade two small bowel toxicity in three (10%) patients. In addition, long intervals between two RT schedules and high brachytherapy dose favoured better outcomes[122]. In a phase III randomized study comparing neoadjuvant CTh followed by surgery versus RT and CTh in FIGO stage IB2, IIA and IIB, 12.3 per cent of patients developed local recurrence only and 6.3 per cent received local and distant post-surgery; around 30 per cent of them received salvage RT[123]. Although the primary analysis showed difference in DFS between the two arms, no difference was seen in OS. Effective salvage of recurrence using RT with or without CTh may be one of the reasons[123]. NCCN 2020[124] and ESMO-ESGO-ESTRO[33] guidelines state that patients with central recurrence, who have not received RT or failed outside the treatment fields, should undergo surgical resection if feasible followed by adjuvant RT (including brachytherapy) if feasible, and systemic therapy. In patients who have received prior RT and have a central recurrence, pelvic exenteration is advised, while in non-central disease, pelvic re-irradiation can be offered or systemic CTh[33,124].

In patients presenting with nodal relapse, surgical debulking, RT with CTh, or best supportive care can be offered; however, the prognosis is variable; with three-year OS rate of patients who underwent RT and CT being 85.7 per cent; surgery 66.7 per cent; CTh only 48.8 per cent; RT only 41.3 per cent and best supportive care 0 per cent ($P$=0.014)[125]. Re-irradiation with or without CTh is feasible without much side toxicity. In a study, 22 cervical cancer patients with LN recurrence post-surgery were treated with salvage RT (median dose 60 Gy) with (n=18) or without (n=4) CTh[126]. Patients treated with CTh and RT achieved a longer five-year PFS 72.9 per cent and OS rate 60 per cent with less than 20 per cent recurrence occurring inside the RT field[126]. In a retrospective analysis of 28 patients with recurrent genitourinary malignancies after a median disease-free interval of 9.5 years, RT to a median dose of 50 Gy using hypofractionated schedule showed good symptomatic relief and no grade 2-4 toxicity[127]. The authors suggested that a median cumulative dose of 100 Gy could achieve successful palliation without much toxicity in a patient previously treated with RT[127]. A clinical trial exploring the role of IMRT in the re-radiation of the pelvis in recurrent cervical cancer is ongoing (NCT03170570). SBRT is an attractive option; it can deliver higher doses using highly conformal RT and in a shorter overall treatment time. SBRT has been tried in para-aortic nodal recurrences from gastric, prostate and gynaecological primaries[128-133] as shown in Table VI. In a study on 91 patients (13% patients had cervical cancer primary) Loi *et al*[134] treated pelvic and para-aortic nodal relapse with SBRT 48 Gy in six fractions (biological equivalent dose of 86 Gy), and showed a median OS of 36 months and PFS of 79 per cent at four years with no late grade three or more toxicity. Park *et al*[82] treated 100 patients of recurrent oligometastatic cervical cancer using SBRT and reported two-year PFS of 82 per cent and OS of 57 per cent. Choi *et al*[132] treated 30 patients using SBRT 33-45 Gy in three fractions with four-year LC and PFS of 67.4 and 45 per cent, respectively, with grade three toxicity occurring in one patient only after 20 months of treatment. Although the evidence in pelvic re-irradiation using hypofractionated SBRT in cervical cancer is emerging, data from other pelvic malignancies have shown promising results[135]. A survey within the EMBRACE network showed that for out-of-RT field nodal recurrences, 63.7 per cent preferred treating with the intent of curing the disease with RT and CTh, while for in RT field recurrences, palliation was the aim of the treatment[34]. Thus, re-irradiation of the pelvis in recurrent cervical cancer is an area of significant uncertainty and further trials are warranted.

**Future considerations**

The ESTRO-EORTC expert groups have classified OMD based on different characteristics of the patients who underwent treatment with curative intent and sub classified into oligorecurrence, oligoprogression and oligopersistence, which is being prospectively evaluated[22]. These authors have started OLIGOCARE project, a prospective project which is currently accruing patients with OMD, where the researcher can follow up their work which will establish further

**Table VI.** Select studies showing outcomes and toxicities of stereotactic body radiation therapy in para-aortic nodal recurrence

| Author (year) | Number of patients | Re-irradiation | Primary cancer | SBRT dose | Outcomes | Toxicity |
|---|---|---|---|---|---|---|
| Bonomo *et al*[128], 2013 | 26 (32 nodes) | Not reported | Gynaecological and prostate | 36 Gy/3# in majority | LC-100 per cent<br>Distant progression in 8 per cent<br>All patients alive till last follow up | No acute or severe toxicity |
| Corvò *et al*[129], 2013 | 33 | 3 ReRT (median previous RT dose-30 Gy) | Pancreas and colon | 35 Gy/5# weekly | LC-83 per cent at 2 years<br>16 patients at median follow-up of 28 months | No acute or late grade 3 or more toxicity |
| Jereczek-Fossa *et al*[130], 2012 | 69, (94 nodes) | 20 lesions | Gastro-intestinal, prostate | 24 Gy in 3# | Three years<br>LC-64.3 per cent<br>OS-49.9 per cent | Late grade 3 or more in 3 patients |
| Kim *et al*[131], 2010 | 7 | No | Gastric | 48 Gy/3# | Three years OS-43 per cent, local relapse in 1 patient | No late toxicity |
| Choi *et al*[132], 2009 | 30 | 4 patients | Cervix, endometrial, gastric | 33-45 Gy/3# | Four years<br>LC-67.4 per cent<br>PFS-45 per cent<br>OS-50.1 per cent | Late grade 3 in one patient |
| Bignardi *et al*[133], 2011 | 19 | No | Miscellaneous | 45 Gy/6# | Two years<br>LC-77.8 per cent<br>PFS-19.7 per cent<br>OS-93.3 per cent | Late grade 3 in one patient |

OS, overall survival; PFS, progression-free survival; LC, local control; RT, radiation therapy; SBRT, stereotactic body radiation therapy; Gy, gray

which treatment is best suited to individual patients (available from: *https://project.eortc.org/e2-radiate/platform/*). A nomogram is also available to stratify oligometastatic patients based on the sex of the patient, timing of presentation of the disease, presence of intracranial metastases, histology and KPS score and to plan individualized care[136]. A recent survey highlighted the need of joint approach and clinical trials to decide the optimal management of OMD and ORD in cervical cancer[34].

## Conclusion

Metastatic cervical cancer possesses a challenge in diagnosis and treatment, and with conventional CTh, the survival remains poor. Treatment intensification using RT in local and metastatic sites, especially SBRT, has shown promising results with improved OS and PFS. As the role of SBRT continues to grow, the utility of this approach in cervical cancer needs to be explored.

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