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Review

What is the evidence for the clinical value of SBRT in cancer of the cervix?

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ABSTRACT

Aim: The aim of this review is to describe and analyze indications and results of the use of SBRT in uterine cervix cancer, reviewing articles published from January 2010 up to August 2017, for any one of the four indications listed:

1 Patient refusal or anatomic impediments to interstitial or intracavitary brachytherapy (BCT), i.e. SBRT as an "alternative" for BCT;
2 Patients with voluminous tumors, or asymmetric tumors where BCT alone would not achieve curative doses, i.e. SBRT as a primary adjunct to BCT;
3 Pelvic and para aortic adenopathy where SBRT could be used as a boost, i.e. SBRT as a primary adjunct to external beam pelvic radiotherapy;
4 Small volume recurrences (postoperative or post radiotherapy), i.e. SBRT for salvage.

Background: Cervix cancer standard treatment involves pelvic irradiation and chemotherapy, recent advances in irradiation techniques might offer new possible approaches.
Material and methods: Systematic review of the English language literature about Cervix cancer, SBRT, published from January 2010 to January 2018 identified through a database search of PubMed, and Ovid MEDLINE, using pre-defined search phrases.
Results: The results in the literature, in general, demonstrate rather weak efficacy of SBRT. In this review, we did not find strong evidence to recommend routine SBRT as a primary treatment for cervico-uterine cancers, i.e. as a replacement for BCT; in highly selected cases it might be considered useful as salvage therapy for relapsed cervix cancer.
Conclusion: The existing data to not warrant recommending SBRT for the definitive treatment of cervix cancer, but may have some value in the recurrent/relapsed setting.

1. Background

The technique of radiosurgery (SRS) consists of delivering high fractional doses of radiation, usually to a small target in a single fraction, with the aim of submillimetric precision, and

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the purpose of ablating the tumor without exceeding tolerance doses of organs at risk (OAR). SRS was initially developed for brain tumors and functional disorders, with the delivery requiring a neuro-navigational stereotactic system. This intracranial SRS technique eventually lead to the evolution of stereotactic fractionated body radiotherapy (SBRT) treatments, wherein instead of a single fraction, a "few fractions" (typically 3–5) are utilized, and frame-based stereotactic navigational approaches are replaced with image, surface, or fiducial-based navigation.[1]

Cervix cancer is the 4th most common cancer in women worldwide.[2] In 2017, ESMO published standardized guidelines for the non-surgical management of cervix cancer.[3] These guidelines recommend pelvic external beam radiotherapy (or extended fields for high-risk, node positive patients) with brachytherapy boost in order to achieve a final total dose of 85 to 90 Gy to the Clinical Tumor Volume. Brachytherapy boost represents the only safe way to deliver such high doses, which correlate with improved local control and survival. Such high dose radiotherapy, based on data from several randomized trials, is delivered concomitantly with chemotherapy, usually on a weekly, low-dose platinoid scaffold.[4,5]

The typical approach to treating cervix cancer with radiotherapy involves whole pelvic irradiation to include the lymph nodes and primary tumor, and sometimes the nodal chain along the para-aortic region. The most frequent grade 3 acute toxicities during radiochemotherapy are hematologic and bowel, both of which can be reduced using intensity-modulated radiotherapy (IMRT). Proton beam therapy, not commonly employed, carries the potential benefit of reducing these bowel and hematologic toxicities. Nodal boost irradiation for macroscopic disease is performed when needed. OARs such as the spinal cord and kidneys are important to consider whenever extended field radiotherapy and/or nodal boost is contemplated. Brachytherapy is tailored to boost the dose to the cervical, paracervical, parametrial, and vaginal disease, balancing the prescription dose with the tolerance of surrounding OARs (small bowel, rectum, sigmoid, and bladder). When inadequate dosimetric coverage of voluminous tumors is identified as a potential limitation, the GEC ESTRO guidelines[6] recommend the addition of interstitial brachytherapy to increase local control and limit OAR doses.

When the performance of brachytherapy is compromised, or the patient refuses brachytherapy, or brachytherapy is unavailable, SBRT boost in lieu of brachytherapy has been used. Despite promising short-term responses to SBRT, about 20–40% of patients eventually develop local recurrence.[7,8] About half of all recurrences from cervical cancer occur in-field, and sometimes this is managed with pelvic exenteration, a highly morbid approach.[9–12] Another salvage approach is ablative irradiation with SBRT, which we will analyze in this article.

2. Material and methods

PubMed Medline and OVID search of articles published in English from January 2009 to January 2018 was conducted, using the following search terms: SABRT, SBRT, Cyberknife, Cervix cancer. All articles, whether review, prospective, retrospective or case reports of treatments delivered with SBRT for Cervix cancer were searched. We limited our search to the most recent 8-year period, given that this coincides with the advent and utilization of chemoradiotherapy as a standard, having replaced, the older, more inferior radiotherapy alone standard.

3. Results

We identified 32 published articles, a majority, in the last 5 years. We categorized these into the following groups, based on SBRT usage intention:

1 Patient refusal or anatomic impediments to interstitial or intracavitary brachytherapy (BCT), i.e. SBRT as an "alternative" for BCT;
2 Pelvic and para-aortic adenopathy where SBRT could be used as a boost, i.e. SBRT as a primary adjunct to external beam pelvic radiotherapy;
3 Small volume recurrences (postoperative or post radiotherapy), i.e. SBRT for salvage.

1 SBRT as an Alternative to Brachytherapy:

SBRT is not an established or accepted alternative to BCT. However, in certain patients, BCT is precluded by coexisting medical conditions, unfavourable anatomy (too close to OARs or unfavourable tumor size in terms of achieving adequate dosimetric coverage; further, some patients occasionally refuse BCT because of its relatively invasive nature. These patients have historically been treated with conventional or IMRT external beam boost instead of BCT.[13,14] In general, the total curative intent dose achieved with this approach is lower than that achieved with BCT. For example, Barraclough et al.,[15] delivered 54–70 Gy total dose with EBRT to patients who had not received BCT. Unfortunately, most of these patients developed a central recurrence in less than 5 years and had a 5 year overall survival of only 49.3%[15]; on the other hand those receiving both pelvic radiotherapy and BCT had superior 5 year local control and much higher 5 year survival of about 70%.[16,17]

In such patients not suitable for brachytherapy, SBRT could deliver a boost to the cervix, more comparable to that achieved with BCT; with modern motion-tracking systems, this is achieved without inordinately large expansion margins for the planning target volume (PTV).[18,19] Another advantage of using SBRT in this context is the ability to keep the total treatment time short, since lengthening treatment duration is known to be deleterious, especially if it extends beyond 7 weeks.[20,21]

Wan et al.[22] performed dosimetric evaluation of HDR BCT versus SBRT in 40 patients with advanced cervix cancer or tumors with asymmetric morphology, and demonstrated dosimetric comparability; this, however, was only an *in silico* study and, therefore, of little clinical utility.

Mahmoud[23] performed a literature analysis from 2003 to 2016, to evaluate bioeffect modeling studies comparing BCT to either conventionally fractionated IMRT as an integrated boost, or to a hypofractionated SBRT boost. All studies required at least 5 patients and only 9 articles fulfilled these require-

Table 1 – SBRT as a boost.

Study	Boost technique	N cervix	MFU (months)	WP total dose (Gy)	SBRT dose/fx	LC % at MFU	% of >GII toxicity
Haas et al. (2012)[24]	SBRT CK	6	14	50.4/61.2	19.5–20/3–4 fx	100	0
Marnitz et al. (2013)[25]	SBRT CK	11	6	50.4	30/5 fx	100	0
Kubicek et al. (2013)[26]	SBRT CK	4	4	45	25/5 fx	75	25
Hsieh et al. (2013)[27]	SBRT HT	9	36	50.4	16–27/5–9 fx	78	0
Mantz et al. (2016)[28]	Not reported	30	62	45	40/5 fx	78.6	0

N cervix: number of patients; MFU: median follow-up; WP: whole pelvis; LC: local control.

ments. Five of these 9 (Haas,[24] Marnitz[25], Kubicek[26], Hsieh[27], Mantz[28]) focused on SBRT boost and were published between 2012 and 2016. This article came to the conclusion that from a bioeffect modeling perspective, SBRT can emulate BCT, but once again, these are purely dosimetric and modeling data, without clinical validation.

We identified 5 clinical reports of the use of SBRT boost instead of BCT boost after pelvic radiotherapy which in total contained 60 cervix patients; these reports are summarized in Table 1. These reports are highlighted below.

In the retrospective series published by Haas et al.,[24] six patients were treated to 45 Gy to the pelvis, plus a conventionally fractionated boost to the cervix and uterus with IMRT to 50, 4 Gy (in one patient) and 61.2 Gy (in 5 patients); the volume of the bladder and rectum receiving more than 70 Gy was limited to < 5% (V70Gy ≤ 5%). After EBRT, patients had 3–4 gold fiducial markers placed in the cervix and upper vagina. SBRT planning with thin slice CT scans (1.25 mm) and MR was performed 1 week after fiducial placement with the patient in the same position as used for the prior pelvic radiotherapy. The gross tumor volume (GTV) was contoured with CT and MRI. All patients received SBRT boost using the CyberKnife system; 5 of 6 received 4 Gy × 5, and the other received 6.5 Gy × 3. No grade 3 or higher rectal or urinary toxicities were reported, but median follow-up was only 14 months. Five of 6 patients with at least 12 months follow-up did not experience relapse.

Jorcano et al.[14] reported results of 17 endometrial and 9 cervical cancer patients treated with postoperative EBRT (45–50.4 Gy) followed by an SBRT boost of 14 Gy delivered in two fractions. With a median follow up of 47 months, the 3-year loco-regional failure-free and overall survival rates were 96% and 95%, respectively. No severe (>grade-3) acute urinary or low-gastrointestinal (GI) toxicity was observed during treatment and up to 3 months after treatment completion.

At the 2017 ESTRO meeting, O'Donnell[29] reported on a National Cancer Database review of patients with cervix cancer treated from 2004 to 2013 with radiochemotherapy plus standard BCT boost ($n = 14{,}394$) or IMRT ($n = 1468$) or SBRT boost ($n = 42$). After matching patient characteristics, only IMRT had significantly lower OS than BCT. The median overall survival was 93.2 months, patients who received BCT boost survived a median of 99 months, patients with SBRT boost survived a median of 30.6 months, and patients who received IMRT boost survived a median of 29.8 months, however, on a multivariable analysis, factors significantly associated with poorer overall survival where: advancing age, having Medicare or Medicaid insurance, a histology of adenocarcinoma, advancing FIGO stage of disease (patients with FIGO stage III-IV disease had poorer survival than early-stage disease), nodal involvement within the true pelvis, presence of metastatic disease, and receiving IMRT rather than brachytherapy. In this article, having an SBRT boost was associated with worse overall survival on a univariate analysis (hazard ratio [HR] = 2.222, 95% CI = 1.360Y3.631, $p = 0.001$) but it was not worse than brachytherapy on a multivariable Cox proportional hazard analysis (HR = 1.142, 95% CI = 0.686–1.901, $p = 0.609$). When Propensity-Matched Analysis was done in 30 patients who received SBRT boost with adequate follow-up (matched with 70 control BCT cases) there was no significant difference in overall survival between those who received SBRT boost and those who received a brachytherapy boost (HR = 1.477, 95% CI = 0.746–2.926, $p = 0.263$).

2 SBRT as treatment for paraaortic lymph node recurrence or as boost:

There are few cases of SBRT utilization reported in this setting for cervix cancer, we report 2 studies in the literature (30 cervix cancer patients).

Choi et al.[30] reported 30 patients with cervix ($n = 28$) or endometrial cancer with macroscopic metastatic para aortic lymph nodes. In 4 cases SBRT was delivered as a complement to EBRT and in 26 SBRT was used exclusively, obtaining 67% local control and 50% OS at 4 years follow up. Only 1 patient developed a late toxicity, 20 months after completion of treatment, a ureteral stricture treated with catheter insertion.

Higginson et al.[31] described a series of 7 patients treated with salvage SBRT for lymph node recurrences in gynecologic cancers, 2 with cervix cancer with macroscopic disease in pelvic and paraaortic areas, where SBRT boost was used. With 18 months median follow-up for the cohort of 7 patients, the rates of one-year loco-regional control, distant failure and overall survival were 79%, 43%, and 50%, respectively.

3 SBRT for salvage:

The local recurrence rate for cervix cancer is 10–20% for early stage disease treated with surgery, or definitive chemotherapy plus radiotherapy with BCT; the recurrence rates increase to 15% for stages IB and IIA and to 20–50% for stages II–III. Conventional treatment used for isolated, non-metastatic, small-volume, central recurrence includes systemic treatment and pelvic exenteration if the patient was previously irradiated. Radical radiotherapy is performed when the first treatment was solely surgery.

Many investigators have reported that lateral recurrences in the pelvis have worse prognosis than central ones.[32–34] This is probably due to the fact that lateral tumors cause symptoms

Table 2 – SBRT for recurrence.

Study	N of patients	Primary disease	SBRT dose (Gy/number of fractions)	Local control	Overall survival	Local toxicity (N of patients/Grade)
Park et al. (2015)[35]	68	Cervix	39/3	79% at 5 years	58% at 2 years	5/GIII
Deodato et al. (2009)[36]	6	All Gyn	20–30/4–6	92% at 1 year	NR (PFS 2 year:81, 8%)	0/>GII
Yazici et al. (2013)[37]	16	Cervix	15–40/3–5	94% at 1 year	60% at 1 year	6/>GIII
Dewas et al (2011)[38]	16	Gyn + Gi + bladder	36/6	51% at 1 year	median OS 11 months	0/>GIII
Abusaris et al (2012)[39]	27	Cervix + other	16–45/2–6	53% at 2 years	NR	0/>GIII
Kunos et al (2012)[40]	16	All Gyn	24/3 fx	100% at 6 months	median OS 20 months	0/>GIII
Choi et al. (2009)[30]	30	Uterus + cervix		67% at 4 years	50% at 4 years	1/GIII
Seo et al. (2016)[41]	23	Uterus + cervix	27–45/3	65% at 2 years	43% at 2 years	3 recto vaginal fistulae

later than central recurrences; another reason is that the laterally located lymphatic network is more extensive, resulting in greater microscopic tumor cell dissemination, causing larger volume recurrences. As a result, there is also a higher risk of distant relapse. When considering BCT as a treatment, it can be very difficult to escalate doses in the lateral areas of the pelvis. It is in these situations that SBRT emerges as an option.

In Table 2, we summarize 8 reports (most of them cervix + other primary tumors) from the literature describing a total of 202 cervix patients who were treated with SBRT for pelvic recurrence.

Seo et al.[41] described 23 cervix cancer patients with local pelvic wall recurrences treated with 27–45 Gy SBRT in 3 fractions of 9–15 Gy. The two-year rates of overall survival, local progression-free survival, and disease-free survival were 43, 65, and 52%; best results were achieved when the GTV was <30 cm^3. Since this is primarily a palliative treatment, symptom resolution/improvement is also an important endpoint. Pain control was reported in 13%, and a reduction in pain medications was achieved in 70% of patients.

Gukenberger[42] analyzed the outcomes of 19 previously treated patients with locally recurrent disease: 12 cervix, and 7 endometrial cancer patients. Sixteen of these patients were treated with whole pelvic irradiation to 50 Gy plus boost. Because of large volume of recurrent cancer (median 4.5 cm) and peripheral location ($n = 12$), stereotactic body radiotherapy (SBRT; median 3 fractions of 5 Gy each to 65%) was used for local dose escalation instead of ($n = 16$) or combined with ($n = 3$) vaginal brachytherapy. Median EQD2 to the recurrent tumor was 68.8 Gy (range 40–75 Gy) considering the conventionally fractionated and the dose at the PTV margin of the SBRT boost. If the dose at the isocenter of the SBRT boost is considered as treatment dose, median EQD2 to the recurrent tumor was 82.8 Gy (range 62.2–93.8 Gy). Median follow up was 22 months, median OS was 25 months, and 3-year overall survival was 34% with systemic progression as the leading cause of death (7 died of systemic progression, 1 died of local tumor progression, 1 of comorbidities and 1 of unknown cause). The 3-year local control rate was 81%. G3-G4 late toxicity rate was observed in 3 patients, 2 suffered from grade IV intestino-vaginal fistula (sigmoidovaginal $n = 1$; recto-vaginal $n = 1$) at 16 and 23 months after salvage radiotherapy. One patient suffered from a grade IV small bowel ileus, six months after treatment. This resulted in a 25% rate of late toxicity >grade II at three years. Similar data have been published in the literature using non-3D image guided BCT ± EBRT for recurrent gynaecological malignancies (late toxicity >grade II in about 20% of the cases). This experience suggests that SBRT for local dose escalation to the residual tumor after conventionally fractionated radiotherapy of the whole pelvis can result in high rates of local control in bad prognosis recurrent patients whenever vaginal brachytherapy alone is inappropriate for boost irradiation, but is also associated with high rates of >grade II late toxicities.

4. Discussion

Therefore, there is clearly a paucity of adequate data that would support routine substituting BCT for SBRT, and its routine utilization should not be encouraged. A US SEER database analysis from 1998 to 2009 showed that there was a tendency to reduce the use of BCT in cervix cancer.[25,27,29] This analysis identified that IMRT or SBRT in lieu of RCT was used mostly for older patients, larger tumor size, stage IVA disease, at treatment centers with a low volume of patients, and at centers with limited facilities. As expected, the use of IMRT or SBRT boost was associated with a higher risk of death, even surpassing the impact of not being able to receive chemotherapy (concurrent with radiotherapy). In an editorial by Eiffel et al.[16,32] worrisome comments were made about the SEER database results reporting the reduced use of BCT, since it has an irreplaceable role in the treatment[27] of these patients with curative potential, and it should clearly not be omitted or replaced by IMRT or SBRT boost, except for very exceptional cases, and even here, one must be ready to accept a probable detriment in outcome.

There are no prospective trials of SBRT in these settings, and no dose-prescription standardization exists. Most of the reports in the literature represent anecdotal usage in small series of patients, either because of patient refusal of brachytherapy, or because brachytherapy was too challenging due to location and/or anatomy, or the patients were too frail to undergo brachytherapy.

The situations in which[43,44] SBRT is used in lieu of BCT as definitive boost are very sparse, and although some so-called promising results are concluded by the authors, long-term efficacy and toxicity remain largely unreported.

In the setting of pelvic sidewall recurrence, limited data suggesting modest efficacy have been reported in the literature, but clearly, it must be borne in mind that only a select subset of patients with small volume recurrences can be managed in this manner, as a large dose per fraction associated with SBRT would likely be too detrimental for patients with large volume recurrences.

Finally, in the setting of macroscopic adenopathy, especially high-pelvic and paraaortic, where BCT is impossible to perform, SBRT might represent a potential approach.[30,31]

5. Conclusion

SBRT is not a replacement or an alternative technology for the management of cervical cancer; technologically and biologically, there is some appeal because of precise delivery, the ability to overcome the impact of motion, and the ability to deliver the total dose in a short schedule to achieve biological comparison to BCT. The literature on this topic is exceedingly sparse; a handful of dosimetric and modeling studies provide limited data and information; the clinical reports are mostly anecdotal and inadequate to base recommendations on.

Conflict of interest

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