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Stereotactic body radiotherapy (SBRT): Technological innovation and application in gynecologic oncology

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ABSTRACT

Objectives. Stereotactic body radiotherapy (SBRT) is a novel form of noninvasive, highly conformal radiation treatment that delivers a high dose to tumor. The advantage of the technique resides in its ability to provide a high dose to tumor but spare normal tissues to an extent not previously possible. In this paper we will provide an introduction and review of this technology with regard to its use in gynecologic malignancies. Preliminary results from our experience are presented for the purpose of illustrating the range of SBRT applications in gynecologic oncology.

Methods. A comprehensive literature review was conducted and our experience from the past three years was reviewed.

Results. Six case series are published that report results of SBRT for gynecologic malignancies. Sixteen gynecologic patients have been treated with SBRT at our institution. Treatment sites include pelvic and periaortic nodes (9 patients), oligometastatic disease (2), and cervical or endometrial primary tumors when other conventional external radiation or brachytherapy techniques were unsuitable (5). Preliminary follow-up at a median of 11 months (range, 0.3–33 months) demonstrates 79% locoregional control, 43% distant failure, and 50% overall survival.

Conclusions. SBRT boosts to macroscopic periaortic node recurrences and other sites seem to provide local control and a possibility of long-term disease-free survival in carefully selected patients. Previously this had been difficult to achieve with conventional radiotherapy because of the proximity of periaortic nodes to small bowel. SBRT also offers a novel approach for minimally invasive treatment in the management of gynecological cancer where current surgical and radiotherapy techniques are unsuitable.

Introduction to radiosurgery

Much of the technological progress in radiotherapy over the last 20 years has been a result of 1) more accurate delineation of a tumor using computed tomography (CT) and magnetic resonance imaging (MRI) and 2) new ways of delivering radiation dose more precisely to a target (usually a tumor) and away from normal tissues. Stereotactic body radiotherapy (SBRT) is a relatively new type of radiosurgery that is capable of precise delivery of converging radiation beams onto a small target in nearly any location in the body [1–3].

Radiosurgery is fundamentally different from conventional radiation therapy (RT) in a few notable ways. Conventional RT delivers daily treatments over several weeks and typically targets visible tumor and subclinical extension of disease, with a surrounding margin to account for unavoidable variations in how the patient lies on the treatment table each day and in the position of internal organs due to peristalsis, respiration, and bladder and bowel filling. The expanded margin around the tumor, however, also leads to more irradiation of normal tissues and related treatment toxicity.

Radiosurgery, by contrast, typically involves treating just the visible tumor on imaging and a smaller margin around the tumor to account for internal target motion. Radiosurgery involves fewer treatments, delivers a higher dose per treatment (up to 20 Gy versus 1.8–2.0 Gy with conventional RT), and utilizes an increased number of radiation beams compared to conventional RT. Radiosurgery for intracranial tumors has been available since the 1960s when the gamma knife system was developed to treat intracranial conditions [4,5]. The gamma knife employs 201 1 mm ^{60}Co radioactive sources, arranged hemispherically around the cranium of a patient who is mechanically secured into a head frame for immobilization. The path of the emitted gamma rays from these multiple ^{60}Co sources

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converge onto a small target within the brain, delivering a high dose to a confined area with submillimeter accuracy [6].

Thus, radiosurgery had its beginnings in irradiating intracranial malignancies because of favorable anatomy: the cranium could be effectively immobilized and the internal organ motion of the brain is limited, allowing precise, safe delivery of high doses. The central challenge of using radiosurgery techniques outside of the brain is the problem of internal organ and target movement due to respiration and peristalsis and the associated safety concerns of using high radiation doses per treatment when there is at least 5–10 mm of uncertainty in the actual location of the tumor [7,8].

Stereotactic body radiotherapy (SBRT)

SBRT is the use of high doses of radiation to small targets outside of the brain. SBRT began in the 1990s, when new devices were developed to dampen respiratory excursion [9] and use imaging technologies to verify a target's location within the patient while the patient is on the radiation treatment table [10,11], allowing the radiation oncologist to more accurately account for internal target and organ movement (reviewed here [1]). The term 'stereotactic' implies the use of a system of 3-dimensional coordinates to localize a region of interest within the body, using either internal or external reference markers. Immobilizing body frames use external references whereas newer systems use either "on-board imaging" or internalized fiducial markers. While different investigators may use varying definitions, the U.S. Medicare statutes define SBRT as consisting of 1–5 treatments.

In some centers, SBRT is performed on the same treatment platform as conventional RT, but with additional "on board" imaging devices to verify patient positioning and intensity modulation to conform dose to the target. For instance, a cone-beam CT can be obtained while a patient is lying on the treatment table about to be treated and the CT images used to compare to the original CT-based radiation plan to assure congruency of the planned versus actual patient position [12]. Some cone-beam CT systems utilize megavoltage (MV) energies using the same linear accelerator source as the therapeutic radiation doses emitted afterwards (Siemens Medical Solutions, Inc., Concord, CA and TomoTherapy Inc., Middleton, WI). Other systems provide higher resolution cone-beam CTs with kilovoltage (kV) energies (Varian Medical Systems Inc., Palo Alto, CA and Elekta AB, Stockholm, Sweden).

Alternatively, small, radio-opaque fiducial markers can be placed directly into the tumor or surrounding tissues. The fiducials are then localized on two dimensional (2D) kV X-rays and the spatial relationship between the markers and between the markers and 2D bony anatomy informs the viewer of the internal location of the target and position of the patient. The real-time tumor-tracking (RTRT) system, developed at the Hokkaldo University School of Medicine in Japan, uses X-rays obtained every 0.03 s to localize fiducial markers and rapidly turns off the radiation beam with only 0.03 s of lag time when the target is outside of the radiation beam [13].

SBRT has met with promising success in treating early T1-2N0 non-small cell lung cancers [14,15], renal cell carcinoma [16], hepatocellular carcinoma [17,18], and low and intermediate risk prostate cancer [19,20], particularly in medically inoperable patients. SBRT has also become a routine way to treat lung, spine, and liver metastases [1].

SBRT in gynecologic oncology

To date, SBRT has been used for gynecologic malignancies in the treatment of macroscopic pelvic and periaortic lymph nodes and oligometastatic disease. Potentially it could be used as a substitute for brachytherapy for some patients if brachytherapy is anatomically or dosimetrically unfavorable. Image guided therapy using cone-beam CT or fiducial tracking is highly advantageous for gynecologic malignancies to account for the significant degree of uterine movement due to bladder and rectum filling/emptying [7,21] and because of the 45–60% tumor regression seen during conventional RT (before SBRT boosts) [7,21,22].

Robotic SBRT

Robotic SBRT uses the same source of radiation as conventional external beam radiotherapy, but the linear accelerator is mounted onto a robotic arm with more degrees of freedom than the circular 360 degree path around the patient on conventional accelerators. The robotic arm is similar to ones used on car manufacturing assembly plants and can move rapidly enough to match changes in a target's position detected by kV X-ray imaging, such as when a lung tumor moves during the respiratory cycle.

The Cyberknife robotic arm device (Accuray Inc., Sunnyvale, CA) allows for the delivery of an increased number of angles of radiation entry into the body and thereby allows a greater multiplicity of converging beams (100–300) [23,24]. By comparison, conventional external beam radiotherapy typically employs only 1–9 stationary beams. The technologic advantage of the multiplicity of beams and the stereotactic tracking allows robotic radiosurgery to employ a smaller margin around a target and therefore less normal tissue receives high doses of radiation. Instead of adjusting the position of the linear accelerator to accommodate internal organ movement like the Cyberknife, the Novalis TX system (BrainLAB) also uses robotic technology to automatically adjust the patient's position. The Novalis system obtains orthogonal 2D X-rays while the patient is on the treatment machine to match digitally reconstructed radiographs derived from the original radiation planning CT [25]. Registration of the two data sets drives the robotic adjustment of the treatment table to bring into agreement the actual and the planned patient position.

Placement of the fiducials into the lung, liver, or other locations can be achieved through percutaneous, CT-guided insertion of the seeds directly to the tumor, typically by interventional radiologists. Alternatively, fiducials can be placed directly into the lung through an endobronchial approach to reduce the pneumothorax risk with a percutaneous approach [26].

Thus there are a number of radiotherapy systems capable of performing SBRT, and no one system can be considered uniformly superior to another [1]. The Novalis, Cyberknife, and RTRT systems each provide rapid fluoroscopic imaging to localize and track fiducial markers, but the Cyberknife lacks 3D information and morbidity can result from internal fiducial placement. The cone-beam CT based systems provide 3D information regarding target position, but the lag time between the CT and treatment start can be minutes in duration and thus there is limited ability to track a target.

Robotic SBRT in gynecologic oncology

In the pelvis, fiducials can be inserted into the cervix, paravaginal and parametrial tissues by gynecologic oncologists or radiation oncologists during an outpatient pelvic examination. Fiducials can fall out of the cervix or move slightly relative to the other fiducials (median 0.8 mm in one study [27]), thus introducing some small errors. In our practice, we obtain a CT for radiation planning about one to two weeks after fiducial placement, which may in theory allow time for the fiducials to settle into a fixed position. A radiation oncologist verifies the position of the fiducials on the planning CT and on 2D X-rays before the first SBRT treatment begins.

Clinical uses: pelvic and periaortic lymph nodes

Small bowel, kidney, and spinal cord are the dose limiting structures of the upper pelvis and abdomen and thus SBRT may play a role in increasing the allowable radiation dose to the nodes while keeping within radiation tolerances of these organs. Traditionally, 45 Gy can be administered to the periaortic lymph node chain to either treat macroscopically positive lymph nodes seen on imaging at initial presentation or isolated periaortic node(PAN) recurrences. This dose would not be considered a curative one for disease at the primary site, i.e. uterus or cervix, and it is hypothesized that a deficiency of radiation dose to the PANs using conventional external beam radiation is responsible for a significant portion of treatment failures for advanced cervix patients [28–30]. PAN involvement also signifies a greater propensity to develop distant metastatic disease, however, locoregional control is still a prerequisite for overall survival.

There are some suggestions in the literature supporting both views. In the GOG 125 study, patients with biopsy confirmed PAN metastases from cervical cancer primaries were treated with 45 Gy and concurrent 5-FU/cisplatin chemotherapy. The three year overall survival was 50% in patients with normally sized nodes on CT but only 27% in patients with enlarged nodes on CT, possibly indicating a deficiency of dose for macroscopic nodes [28]. However, distant failure was also high — 42% in all 86 patients. In the RTOG 01-16 study, 26 patients with positive periaortic nodes were administered 45 Gy with 3D conformal boosts to 54–59.6 Gy. Despite the boost dose above 45 Gy, PAN persistence or recurrence was thought to be the primary pattern of failure as 11 of 16 failures on CT at 4 months had a component of PAN failure and 10 manifested PAN only failure [29]. In a retrospective review of 198 patients at MD Anderson with regional failures after definitive radiation for cervix cancer, 58% experienced in-field nodal failures [30]. Of all the locoregional recurrences(LRR) recorded from 1980 to 2000 (1894 total patients, 452 LRRs), 43% were node only failures and 72% of LRR had some component of nodal failure. Thus, in the primary setting, in-field nodal failures due to a deficiency of dose remain an important component of the overall failure pattern while the risk of distant failure is also high (at least 42% in GOG 125) [28].

In the salvage radiation setting for isolated PAN recurrences, the overall survival with radiation alone is only 0–19% (see Table 1) [30,31]. These numbers may have improved somewhat because of the advent of concurrent chemotherapy [32–34] and more optimal patient selection with CT-PET imaging. Taken together, these results suggest that a deficiency of dose to the PAN may be responsible for significant numbers of locoregional recurrences in the primary setting and for poor results in the salvage setting.

Boosting radiation dose above 45 Gy to the periaortic nodes with conventional external beam radiotherapy is associated with increased toxicity in multiple studies. Just 45 Gy results in at least 14% late grade 3–5 toxicity [28,35] and efforts to boost the PA nodes to a higher dose (54–59.6 Gy) with 3D conformal radiotherapy were met with 40–50% grade 3–5 toxicity [29,36]. In RTOG 01-16, 40% late GI toxicity was observed, with 8 patients requiring subsequent surgery [29].

SBRT for pelvic, periaortic nodes

SBRT provides a mechanism to boost macroscopic periaortic nodes to a higher dose. Choi et al. reported the first results of this technique with 30 patients (28 cervical, 2 endometrial) receiving Cyberknife robotic SBRT [37] (See Table 3). In each patient, gold fiducials were placed percutaneously, two each to three successive vertebrae near the target. The radiation target was defined as the visible tumor plus 2 mm of margin. Four of the 30 patients received 27–45 Gy of conventional RT to the periaortic LN chain in addition to SBRT. The remaining 26 patients received SBRT alone using doses of 33 to 45 Gy in 3 fractions, prescribed to the 73 to 87% isodose lines. The high dose per fraction with SBRT results in a much greater effective total dose than 45 Gy of conventional RT. The overall local control at 4 years was 67%, progression free survival was 63%, and overall survival was 50%. Larger target volumes corresponded to worse disease free survival: 26 versus 65% for planning target volumes more or less than 17cc. Symptomatic patients, i.e. those with leg edema or lower back pain, exhibited less favorable 4 year overall survival (19 versus 64%), a finding seen in other series [31,32]. Toxicity was limited to 5 cases of grade 3 hematologic toxicity in patients who had received concurrent or adjuvant chemotherapy and one case of ureteral stricture [37].

Two other groups have reported the use of SBRT for isolated periaortic nodes from non-gynecologic malignancies. Kim et al. found that although only one of seven patients with colorectal primaries failed locally after SBRT to an isolated node, five of the seven failed in the periaortic node region or distantly. One patient developed a grade IV bowel obstruction [38]. Similarly, the group treated 7 patients with isolated periaortic nodes from gastric primaries and five achieved a complete response, but only two patients remained alive without disease at 26 month follow-up [39]. Bignardi et al. reported SBRT results from 19 patients with a variety of primary malignancies and unresectable abdominal and periaortic nodal metastases and again,

Table 1
Salvage radiotherapy for isolated periaortic node recurrences.

First author	Patients	Final dose to PAN (Gy)	Chemotherapy	N	F/u	LRF	OS	Grade 3–5 toxicity
Conventional RT								
Chou [24]	Cervical	45	Concurrent cisplatin.	14	5 y	–	51%	NS
Singh [25]	Cervical	45–50.4	Concurrent navelbine, irinotecan, or cisplatin.	7	5 y	–	100	1 pt: grade 3 enteritis
Kim [26]	Cervical	60	Concurrent paclitaxel or cisplatin.	12	3 y	67%	19	2 pts: grade 3–4 hematologic toxicity
Grigsby [23]	Cervical	46.4[a]	No chemotherapy.	20	5 y	–	0	NS
Beadle [22]	Cervical	NS[b]	NS	17	5 y	NS	4	NS
SBRT								
Choi [29]	Cervical (28), endometrial (2).	33–45 in 3 fx[c]	Cisplatin based chemotherapy.[d]	30	4 y	33	50	5 pts: grade 3+ hematologic toxicity; 1 pt: ureteral stricture
UNC series	Cervical (2), endometrial (3), ovarian (2)	20–30 in 4–5 fx[e]	Mixed usage[f]	7	18 m	33	57	None

PAN: periaortic nodes. F/u: follow-up. LRF: locoregional failures. OS: overall survival. RT: radiotherapy. SBRT: stereotactic body radiotherapy. Fx: fractions. NS: not stated.
[a] Median dose.
[b] Treatment patterns were unstated.
[c] 26 patients received SBRT alone while 4 patients received 27–45 Gy of conventional RT in addition to SBRT.
[d] 25 patients received chemotherapy: 2 before SBRT, 14 after SBRT and 9 concurrently.
[e] 4 patients received conventional RT to the periaortic node region as well as SBRT (3 received 45 Gy, 1 received 46 Gy) and three patients received SBRT only.
[f] 1 patient received concurrent cisplatin (cervical), 5 of the 6 other patients received chemotherapy before SBRT.

Table 2
The treatment of oligometastatic disease in gynecologic malignancies.

Author	Patients	N	F/u (y)	5 y OS	Toxicity	Comments
Lung resections						
Clavero [63]	Endometrial (60), cervical (7), ovarian (2), vaginal (1)	70	3	47%	1 death, 26% complication rate	Median DFS 8 months; 8 pts disease free
Yamamoto [64]	Cervical (29)	29	4.3	33	NS	42% 5y DFS in 23 pts with 1–2 mets.
Lim [69]	Cervical (23)	23	1.5	88[a]	No mortalities, 26% complication rate	16 pts disease free[a]
Anraku [65]	All	133	3.3	55	1% mortality, 1% morbidity	25 pts alive with >8 y follow-up
	Cervical squamous	58		47		
	Cervical adeno.	13		40		
	Endometrial adeno.	23		76		
	Choriocarcinoma	16		87		
	Leiomyosarcoma	11		38		
Logmans [67]	Cervical (4), endometrial (1), ovarian (1)	6	3.7	100[b]	NS.	5/6 patients have no evidence of disease with 3.1 to 4.5 years f/u
Liver resections						
Lim [66]	Ovarian	14	2	51	No mortalities, 11 complications	23% 5 y PFS
Chi [68]	Cervical (2), endometrial (2), ovarian (7), fallopian tube (1)	12	2.1	50[c]	No mortalities, 8% complications	3 patients NED at 8, 17, 38 months.

F/u: median follow-up. OS: overall survival. NS: not stated. DFS: disease free survival. PFS: progression free survival. NED: no evidence of disease.
[a] At 18 month median follow-up.
[b] At 3.7 year median follow-up.
[c] Estimated from Fig. 1 at 24 months.

the local control was excellent (78% at 2 years), but the overall progression-free survival was only 20% [40].

We have treated 7 patients with Cyberknife SBRT with isolated periaortic node recurrences (cervix-2 pts, endometrial-3 pts, and ovarian-2 pts). Four of the 7 patients received 45-46 Gy of conventional EBRT in addition to radiosurgery. Doses have ranged between 30 Gy in 5 fractions to 20 Gy in 4 fractions, prescribed to the 58–80% isodose lines (see Figure 2). Three patients have no evidence of disease (NED) at 10, 18, and 19 months follow-up (patients 1, 2, and 8 in Table 4). Two of the three patients which did not receive 45 Gy of conventional RT to the PAN region developed subsequent new PANs outside of the area treated with SBRT. At least two patients developed systemic failures and one is deceased with an unknown pattern of failure. No grade 3–5 toxicity has been noted.

We have also treated two patients with pelvic nodes, one at primary presentation and one at the time of recurrence. Both are alive with no evidence of disease at 5 and 24 months (patients 4 and 7, Table 4). Three of the four endometrial cancer patients treated have NED at 5, 10, and 18 month follow-up.

The reported local control using SBRT is excellent while the competing risk of distant metastases or failure at other sites is also significant. Without local therapy to isolated periaortic node recurrences, few if any long term survivors would be expected. If with longer follow-up, a minority of patients still maintain disease-free survival with a reasonable risk of morbidity, then the technique should be considered efficacious. With improvements in systemic therapies to control distant metastases, locoregional control of macroscopic disease will receive greater attention.

Oligometastatic disease

Oligometastatic disease is a term used to describe a disease state in which limited sites of metastatic disease may still be addressed definitively with local therapy. Conceptually, this term applies to at least three general situations in which local therapy may have a benefit.

First, for chemosensitive malignancies, such as colorectal and breast cancer, patients may be left with few, isolated sites after their primary tumors have been removed (i.e. bowel resections,

Table 3
The use of SBRT for gynecologic malignancies.

Author	Histology (no. of pts)	Sites treated	SBRT dose Gy/fx (no. of pts)	N	F/U (m)	LRF	OS	Grade 3–5 toxicity (no. of pts)
Choi [29]	Cervical (28), endometrial (2)	Periaortic node recurrences	33–45/3[a]	30	48	33%	50%	Grade 3 hematologic toxicity (5), ureteral stricture (1)
Deodato [72]	Cervical (4), endometrial (3), ovarian (4)	Pelvic, mediastinal, inguinal lymph nodes; cervix/vagina; liver, adrenal mets.	20–30/4–6	11	19	33	64	None
Gucken-berger [78]	Cervical (12), endometrial (7)	Pelvic recurrences after prior surgery (12), surgery and RT (6), or RT alone (1)	15/3(16), 30/3(2), 28/4 (1)[b]	19	22	29	34	Grade 4 intestino-vaginal fistula (2), grade 4 small bowel ileus (1), grade 3 urinary frequency (1).
Kunos [80]	Cervical (1), endometrial (1), ovarian (3)	Proximal vaginal recurrences	15–24/3[c]	5	9	20	80	Grade 3 fatigue(1)
Kunos [79]	Vulvar	Labial lesions (3) and pelvic nodes (1)	24/3[d]	3	3	100	100	Vesicovaginal fistula (1)
Molla [77]	Cervical (7), Endometrial (9)	Final adjuvant boost to upper vagina, parametria after prior surgery (14) or for local relapse (2) after surgery or RT	14/2(12), 20/5(3), 40/10(1).	16	13	6	100	Grade 3 rectal bleeding (1)

EBRT: external beam radiotherapy. SBRT: stereotactic body radiotherapy. Fx: fraction. Mets.: metastases.
[a] 26 patients received SBRT alone while 4 patients received 27–45 Gy of EBRT in addition to SBRT.
[b] 16 patients received 46–52 Gy of pelvic EBRT followed by a 15 Gy SBRT boost. Three patients received SBRT alone (30 Gy in 3 fx or 28 Gy in 4 fx). 22 month median follow-up.
[c] Two patients received 45 Gy of pelvic EBRT in addition to SBRT and the remaining three had had prior radiation to the pelvis. 9 month median follow-up.
[d] All three patients had had prior chemotherapy and radiation to the pelvis (36 to 74.6 Gy). SBRT alone was given in an attempt at salvage.

mastectomies) and chemotherapy has cytoreduced microscopic sites of disease. For instance, a plurality of patients with colorectal cancers and liver metastases can still be cured with hepatic metastasectomies [41–43] or even with limited surgical resection of lung, adrenal, and liver metastases in various combinations [44].

Second, for malignancies less chemo- or radio-responsive, local therapy may be the most efficacious option available. For instance, pulmonary metastasectomy for soft-tissue sarcoma [45], melanoma [46], and renal cell carcinoma [47,48] have long been considered an acceptable option and produce long term disease control or cure in a plurality of patients.

Third, sometimes small, limited sites of disease can themselves be life threatening and merit local treatment, such as isolated brain metastases. Radiosurgery or surgical resection of a single brain metastasis can prolong life by about two months compared to whole brain radiation alone [49,50]. Cytoreductive nephrectomy for metastatic renal cell carcinoma may prolong survival, possibly by preventing intraperitoneal hemorrhage [51,52].

Because SBRT can be used to control small metastases in most body sites, its use in oligometastatic disease settings has increased. Single institution series and phase II multicenter trials demonstrate that SBRT can result in excellent local control of liver and lung metastases on the order of 71–96% local control with 1–2 year follow-up [53–58]. Whether such efforts actually improve overall survival is difficult to assess without phase III trials because most patients selected for these phase II trials have already demonstrated long term survival before referral and thus their tumors likely have favorable biological characteristics. In addition, patients selected for phase II trials with limited metastatic disease may have been considered to have earlier staged disease in prior treatment eras when staging imaging was less sensitive. However, with sufficient patient numbers and long enough follow-up, non-randomized data can demonstrate efficacy if the number of long-term disease-free survivors surpasses historical expectations. Such has been the case for colorectal liver metastasectomy patients, with some series reporting up to 26% survival at 10 years — results that are difficult to dispute [59].

SBRT is one of several treatment modalities capable of treating oligometastatic disease. Radiofrequency ablation (RFA) can also treat lung and liver metastases with excellent local control (47–96%) [60–65]. RFA best treats peripheral lesions under 3 cm in size, both in the lung and liver, whereas SBRT can treat lesions up to 6 cm [60,66,67]. In the liver, central lesions close to major vessels are less attractive for

Table 4
SBRT used for gynecologic malignancies or sites of disease at the University of North Carolina.

Pt. no	Age	Histology	Clinical setting	DFI (m.)	RT (Gy)	SBRT (Gy/fx)	F/u (m.)	LR control[a]	Systemic failures[b]	Status	Toxicity[c]
Pelvic and periaortic nodes											
1	63	Endometrial[d]	PAN recurrence	29	–	30/5	10	–	–	NED	None
2	56	Endometrial[d]	PAN recurrence	18	45	25/5	18	–	–	NED	None
3	77	Endometrial[d]	PAN recurrence	22	46	20/4	6	Unknown	Unknown	Dead	Acute grade I diarrhea/loose stools and grade 2 abdominal pain
4	51	Endometrial[d]	Pelvic node recurrence	72	45	25/5	5	–	–	NED	Acute grade I abdominal pain
5	44	Cervix[e]	PAN recurrence	35	45	30/5	3	–	Malignant pleural effusion @1 m.	DOD	None
6	33	Cervix[e]	PAN recurrence	35	–[f]	30/5	25	New PAN @7 m.	–	DOD	None
7	40	Cervix[e]	Pelvic node at initial dx	–	54	12/3	24	–	–	NED	None
8	77	Ovarian[d]	Isolated PAN	42	45	25/5	19	–	–	NED	None
9	50	Ovarian[d]	Isolated PAN	72	–	30/5	33	New PAN @10 m.	Porta hepatis nodes @10 m.	AWD	None
Oligometastatic disease											
10	59	Uterine stromal sarcoma	T8, T11 bone lesions	11	30	25/5	0.3	Unknown	Brain mets. @10 days	DOD	None
11	65	Cervix[e]	Solitary lung lesion	23	–	54/3	21	–	New lung nodules @2 m.	AWD	None
Substitute for brachytherapy											
12	89	Endometrial[d]	Medically inoperable, could not tolerate brachytherapy	–	48.8	20/5	8	–	Unknown	Dead	Late grade 3 rectal bleeding
13	67	Vaginal[e]	Periurethral location	–	45	25/5	22	–	Lung mets. @17 m.	DOD	Acute grade 2 radiation cystitis
14	62	Vaginal[e]	Prior cervical ca. in 1981. Now upper vaginal cuff disease.	–	40	25/5	7	@5 months	–	DOD	None
15	77	Urothelial carcinoma of the bladder	Recurrent disease at vaginal apex after prior cystectomy	6	45	16/4	12	–	–	NED	None
16	51	Cervix[e]	Recurrent disease within vaginal cuff after prior chemoradiation	34	–	25/5	10	–	Liver mets. @2 m.	DOD	None

DFI: disease-free interval before SBRT. F/u: follow-up. RT: conventional radiotherapy. Fx: fractions. LR: locoregional. Mets.: metastases. NED: no evidence of disease. AWD: alive with disease. LR: locoregional. DOD: dead of disease.

[a] Local control defined as progressive disease by RECIST v1.1 criteria using subsequent CT or PET-CT for patients 1–11. Patient 12 had a negative transvaginal ultrasound and normal examination shortly before death. Patients 13–16 were assessed by physical examination. Patients 6 and 9 developed new PANs which were distinct from those treated with SBRT. "–" signifies LR control. When imaging or follow-up examination not available, "unknown" is designated. Time to failure after SBRT is designated as @× months.

[b] "–"signifies absent distant metastases on subsequent CT or PET-CT imaging. When subsequent imaging is not available, "unknown" is designated.

[c] RTOG Acute Radiation Morbidity Scoring Criteria used for symptoms occurring from day 1 to day 90 following SBRT. RTOG/EORTC Late Radiation Morbidity Scoring Schema used for symptoms occurring on day 91 and afterwards.

[d] Adenocarcinoma.

[e] Squamous cell carcinoma.

[f] Patient 6 received prior conventional RT to the PAN region in 2003. SBRT performed in 2008 for an isolated recurrence.

RFA because the circulating blood functions as a heat sink, decreasing the efficiency of thermoablation. In the lung, both RFA and fiducial placement for SBRT carry a 28–45% risk of pneumothorax and a 10–30% need for chest-tube placement [61–63]. SBRT for lesions close to the pulmonary hilum results in an increased risk of bronchial stenosis, although some series suggest reasonable morbidity with decreased doses [68,69].

SBRT for oligometastatic disease in gynecologic oncology

The treatment of oligometastatic disease has become more common in gynecologic oncology and is a category 2A recommendation in the National Clinical Cancer Network guidelines for cervical carcinoma and uterine sarcoma [70]. In some ways, the treatment of oligometastatic disease for ovarian cancer is also commonplace, i.e. when debulking surgeries or bowel resections are performed or when liver metastases are removed.

Is there evidence that patients with oligometastatic gynecologic malignancies may benefit from local therapy? The available data is primarily from surgical series of pulmonary or liver resections of isolated metastases (see Table 2). Calvero and colleagues performed 70 pulmonary metastasectomies and at least eight of whom were rendered disease free [71]. Yamamoto reported a 42% 5 year disease-free survival after surgery in 23 cervical cancer patients with 1–2 pulmonary metastases [72]. Anraku et al. reported 45% 10 year overall survival in 133 patients with mixed histologies after metastasectomies [73]. Lim reported that patients with ovarian cancer patients and parenchymal liver metastases do just as well as stage IIIC patients if a complete resection of hepatic disease is performed — 23% 5-year progression free survival [74]. Taken together, these series indicate that most patients fail distantly after metastasectomy, but a minority of patients can enjoy long term disease free survival or cure after a local therapy [75–77].

In our practice, we offer Cyberknife (CK) SBRT to patients with gynecologic malignancies and 1 to 3 brain metastases. This approach is supported by randomized evidence of a survival benefit and concerns about the treatment related side effects of whole brain radiation [49,78,79]. We have also offered CK SBRT for patients with isolated sites of disease in other body sites with mixed results (See Table 4). Patients 1, 2, 4, 8, 10, and 11 (Table 4) received SBRT to isolated metastases. Four patients have no evidence of disease with up to 19 months of follow-up, and two patients died shortly after SBRT from new distant metastases.

These results highlight the difficulty of assessing the efficacy of this approach and the importance of patient selection. Patients tend to be highly heterogeneous with a wide range of disease free intervals before treatment and large variations in treatment before and after radiosurgery. Only with larger numbers and longer follow-up can the efficacy of SBRT in terms of overall survival be estimated. In the meantime, SBRT can be thought of as a reasonable substitute to surgical metastasectomy for patients who are unresectable or otherwise prefer not to undergo surgery [80]. The cost of a course of SBRT in the U.S. is at least $11,000 in two reports [81,82] and there can be side effects affecting the quality of life. Thus patients should be carefully selected through multidisciplinary discussion, taking into account the disease-free interval before recurrence, performance status, co-morbidities, and results of recent, thorough restaging studies. When local management of oligometastatic disease is selected as the preferred treatment option, surgery, SBRT, and RFA each play a major role, with medical operability, lesion size and location constituting the major variables.

Substitute for brachytherapy

In gynecologic radiation oncology, brachytherapy has an important role in cervical, endometrial, and vaginal carcinoma as a final radiation boost dose after a course of external beam radiation. Brachytherapy holds two advantages over external beam radiation: 1) the radiation sources are placed internally, in close physical proximity to tumor or to tissue at risk for recurrence, thereby sparing

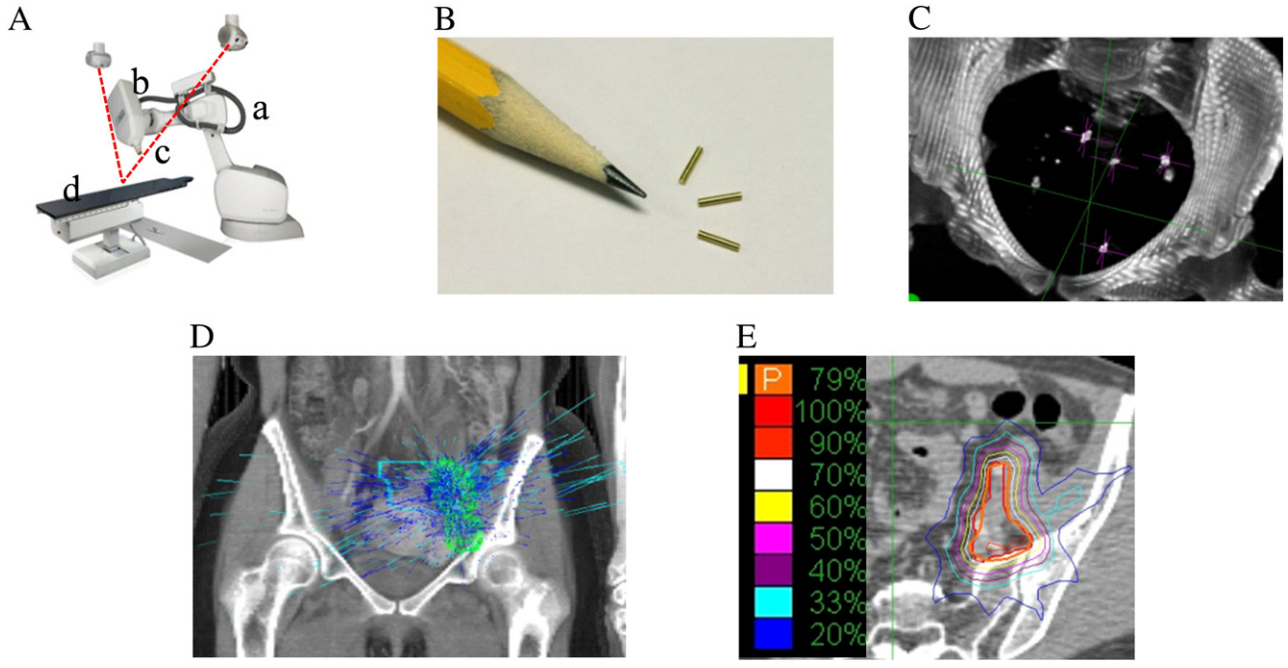

Fig. 1. (A) Schematic of the Cyberknife robotic stereotactic radiosurgery system (image used with permission from Accuray, Inc.). A small, condensed linear accelerator (b) is mounted onto a robotic arm (a). Orthogonal kV X-rays (c) are emitted from sources attached to the ceiling and localize internal fiducial markers. The patient lies on the treatment table (d). (B) Gold Cyberknife fiducial markers. (C) Fiducials localized by 2D X-rays. (D) Coronal view of low dose radiation beams from >100 different converging angles of approach. Each dark blue line marks the course of an anterior-to-posterior beam and the light blue lines mark posterior-to-anterior beams. (E) SBRT radiation plan used for the patient in panel B (patient 7 in Table 4) with superimposed isodose lines on the CT image.

normal tissue and 2) the brachytherapy devices immobilize the areas being treated, greatly reducing the uncertainty involved with internal organ movement and external beam radiation. It would not be expected that SBRT could provide equivalent dosimetry or immobilization compared to brachytherapy. However, there are some patients who cannot tolerate brachytherapy or whose internal anatomy is unfavorable for intracavitary brachytherapy, such as those with non-canalizable cervical ossa, or stenotic vaginas or those with large tumors extending to the pelvic sidewall. In our view, interstitial brachytherapy by experienced practitioners remains the standard option for tumors in these difficult anatomic positions [83–86], but not all investigators agree on its efficacy and even interstitial brachytherapy cannot be employed for those with rectovaginal septum involvement [84]. The technique is technically challenging, highly invasive and has not fully disseminated into routine use in the U.S. as evidenced by one patterns of care analysis which found only 1% utilitization in community practices versus 9% in academic centers [87].

As an alternative option if brachytherapy (either intracavitary or interstitial) is impossible, SBRT may be substituted for brachytherapy to boost gross disease, much like 3D conformal EBRT and intensity modulated radiation therapy (IMRT) have been used [88,89]. Molla and colleagues used SBRT in lieu of brachytherapy as a final boost after EBRT in 16 patients, nine with endometrial and seven with cervical cancer [90]. Fourteen of these patients had prior surgery and thus the treatment was indicated as part of adjuvant therapy to reduce the risk of recurrence. Two patients had recurrent, gross disease after prior surgery or radiation. Twelve patients also received whole pelvic radiotherapy (45–50.4 Gy). For SBRT, each patient was immobilized with a body cast and 5–7 metallic markers were affixed to the skin of the abdomen and localized reproducibly via infra-red cameras. Most patients received 14–20 Gy of SBRT in 2–3 treatments. At a median of 13 months follow-up, there was only one recurrence and one episode of grade 3 rectal bleeding. A low rate of recurrence, however, would be expected in these patients without SBRT because of the low recurrence risk after surgery and post-operative whole pelvic RT for endometrial and cervical cancer.

Other groups have explored the use of SBRT in the recurrent disease setting. Guckenberger and colleagues treated 19 patients with pelvic recurrences after prior surgery (12), surgery and radiation (6), or radiation alone (1) [91]. Pelvic sidewall extension or large tumor size were cited as reasons for inclusion on the study and for SBRT as opposed to vaginal brachytherapy. Most patients were first treated with conventional RT to the tumor and regional lymphatics to a median dose of 50 Gy. Patients then received 15 Gy in 3 treatments of SBRT using a body cast for immobilization and cone-beam CT for verification of position. Three patients received SBRT only because of prior pelvic irradiation (these were given 30 Gy in 3 treatments or 28 Gy in 4 treatments). At a median follow-up of 22 months, the 3 year overall survival was 34%. Seven of 10 deceased patients died of systemic disease. Three local failures were noted in the pelvis. One patient experienced acute grade three urinary frequency, two patients developed late intestino-vaginal fistulae, and one patient developed a grade 4 small bowel ileus. Two of the three patients experiencing a major late toxicity had received prior irradiation.

Other investigators have reported significant toxicity in using SBRT in the recurrent setting after prior irradiation. Kunos et al. attempted to use Cyberknife SBRT to salvage vulvar squamous cell carcinomas that recurred within the labia after all surgical and conventional RT options were exhausted [92]. All three patients recurred locally and one patient developed a fistula. Kunos also reported the use of SBRT for recurrent pelvic tumor after prior irradiation [93]. Three patients had prior pelvic RT only and two patients had prior pelvic RT and brachytherapy. One patient recurred in the distant vagina, two patients recurred distantly, and two patients had no evidence of disease at 6 and 10 months.

In our practice, we have used Cyberknife SBRT when patients have no reasonable option to receive brachytherapy. Three patients (patients 14–16 in Table 4) received SBRT to vaginal cuff lesions (vaginal, bladder, and cervical primary lesions) too large for vaginal cylinder brachytherapy, which is commonly prescribed to only 5 mm depth into the mucosa. Interstitial brachytherapy would also have been difficult for these patients because it would involve placement of catheters directly into the cuff where it appeared that loops of small bowel or sigmoid colon were adhered. We have also treated one patient with a periurethral vaginal squamous cell carcinoma (patient 14) and another (patient 12) who could not receive surgery or tandem and ovoid brachytherapy because of her advanced age and frailty.

The efficacy of SBRT as a boost must be evaluated with the understanding that SBRT currently is reserved for difficult clinical situations, i.e. either recurrent disease after prior irradiation or tumor too large or anatomically difficult for brachytherapy, and that many of these patients have no other treatment option. Early results from the Guckenberger, Kunos, and our group suggest that SBRT can offer local control in some patients. However, when patients have received prior irradiation (i.e. prior external RT and brachytherapy), then SBRT, despite its tight conformality, is still associated with significant morbidity. In addition, SBRT may not be biologically favorable in some circumstances, depending on the proximity of the target to normal structures.

Conclusions

SBRT is an innovative, noninvasive irradiation technique capable of greater treatment accuracy compared to conventional irradiation

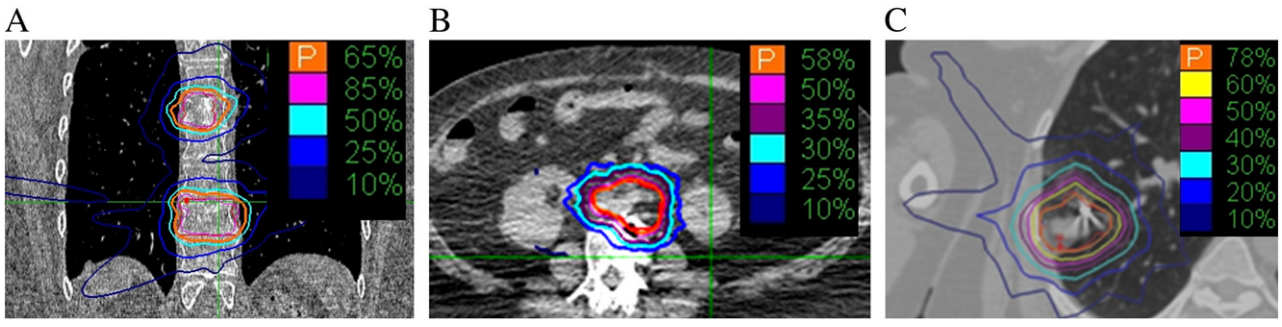

Fig. 2. CT images with superimposed isodose lines that describe distribution of radiation dose. In SBRT, a prescription of dose is specified to an isodose line. Areas inside of that isodose line receive more radiation than the prescribed dose and areas outside of the line receive less dose. The patient in A received 25 Gy to the 65% isodose line (orange) in 5 fractions. A: T8, T11 bone metastases from uterine stromal sarcoma (patient 10 in Table 4). B: Periaortic node recurrence, endometrial primary (patient 2 in Table 4). C: Isolated pulmonary metastasis, cervical squamous cell carcinoma primary (patient 11 in Table 4).

through the assistance of new imaging devices to localize and track a treatment target. In gynecologic oncology, the technique may constitute a more efficacious way to adequately irradiate macroscopic pelvic and periaortic nodes in selected patients with acceptable toxicity. SBRT has already become a part of the management of oligometastatic gastrointestinal malignancies and should be considered one of several local therapy options for carefully selected gynecologic patients. The selection of patients for oligometastatic disease treatment needs to take into account the competing risk of occult systemic disease and the promise of SBRT to provide local control can be explored through multidisciplinary discussion, PET-CT imaging prior to SBRT, and consideration of the disease-free interval before recurrence. In view of the cost of the treatment and safety concerns about high doses per fraction, these patients should be aggressively followed, such as in prospective registry trials, as the ultimate efficacy of SBRT can only be determined with long-term follow-up.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

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