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Various substitutes of brachytherapy boost after neoadjuvant chemoradiation for locally advanced cervical cancer. Literature Review

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ABSTRACT

Objective: Concurrent chemoradiotherapy (CCRT) is widely regarded as the gold standard for locally advanced cervical cancer (LACC). Radio Therapy encompasses pelvic external beam radiation therapy (EBRT), followed by intracavitary brachy therapy (BT) to boost the cervix. However, in developing countries, there is a tendency to prefer surgery over other types of treatments for several reasons - surgery is easily obtainable, more acceptable, and understandable culturally. On the other hand, in developed countries, The utilization of brachy therapy (BT) to boost the cervix in patients with Cervical Cancer (CC) has been gradually declined because of the advent of sophisticated techniques for EBRT. Recently, the treatment of LACC has been a point of controversy. We have no prospective data to justify that surgery or modern EBRT can be used in place of intracavitary BT boost in women with locally advanced CC. This study aims to review existing information about brachytherapy alternatives after neoadjuvant chemoradiation.

Material and Methods: An electronic search of the PubMed database was conducted to obtain key cervical cancer literature. The MEDLINE/PubMED (www.ncbi.nlm.nih.gov) database was chosen as it remains the most widely used resource for medical literature. Additional records were searched in other resources.

Results: The first phase of screening identified 18 articles for the first search term ("Adjuvant hysterectomy" AND "Cervical Cancer"), 10 article for the second search term ("IMRT boost" AND Cervical cancer") and 11 articles for the third search term ("SBRT" AND "Cervical Cancer"). In sum 39 articles were identified to be relevant for the second phase of screening. Studies that included less than five patients with investigated intervention or did not provided enough information about at least one primary endpoint were excluded. A total of 20 (11-adjuvant hysterectomy, 4-IMRT boost, 5-SBRT boost) papers met the selection criteria and were found eligible for this review.

Conclusion: When all these alternative approaches to ICB are evaluated, adjuvant hysterectomy appears to have treatment outcomes comparable to standard of care, while SBRT appears to have only modest yearly results. As a result, the majority of writers believe that neoadjuvant chemoradiation followed by radical surgery or SBRT may be a realistic therapeutic option for patients with LACC, not merely when ICB is unavailable, technically impractical, or rejected. Large, randomized-controlled trials are required to conclusively demonstrate or invalidate non-ICB alternatives for cervical cancer treatment.

Keywords: Cervical Cancer, Adjuvant hysterectomy, IMRT Boost, SBRT boost, Brachytherapy boost.

Review Article

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INTRODUCTION

Until the early nineteenth century, cervical cancer (CC) therapy was limited to surgery. People thought that the entire site of the disease had to be excised. The need for a very aggressive radical surgery had been mostly emphasized in locally-advanced cervical cancers (LACC) patients (1).

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Marie and Pierre Curie's discovery in 1898 was the game changer point. One of the first published climes to the use of radium was that of Margaret A. Cleaves (1848 - 1917) of New York. She treated a patient with LACC with sealed glass tubes of radium through the vagina. In the 1910s, the American surgeon Robert Abbe (1851–1928) made a vaginal applicator for CC (2). As time passed, radiation therapy (RT) became a respectful part of CC therapy, and soon after, all patients with LACC, regardless of age or operability, were assigned for primary irradiation.

Based on a series of GOG (Gynecologic Oncology Group) clinical research findings that published in 1999 National Cancer Institute (NCI) was issued a notice which suggesting RT in conjunction with concurrent chemotherapy instead to RT alone for patients with a variety of clinical situations (for both locally progressed and post-radical hysterectomy patients). As a result of a randomized research demonstrating its lack of benefit over survival, adjuvant extra-facial hysterectomy has been steadily phased out for bulky or 'barrel' shaped cervical cancers. Patients with early-stage cervical cancer are regarded to be the ideal candidates for surgery, while LACC surgery is accepted only for salvage treatment. Even though it is known that optimal chemoradiation therapy is unable to sterilize pelvic lymph nodes in around 16% of cases which may suggest a therapeutic role for adjuvant hysterectomy, systematic pelvic lymph node dissection became a diagnostic/prognostic procedure, and its therapeutic potential has been reported only in metastatic bulky lymph nodes (3-5).

Nowadays, Concurrent chemoradiotherapy (CCRT) is widely regarded as the gold standard for LACC. RT encompasses pelvic external beam radiation therapy (EBRT), proceeded by intracavitary brachy therapy (BT) boost to the cervix (6). However, in developing countries, there is a tendency to prefer surgery over other types of treatments for several reasons - surgery is easily obtainable, more acceptable, and understandable culturally. On the other hand, in developed countries, the utilization of BT to boost the cervix in patients with CC has been gradually declined because of the advent of sophisticated techniques for EBRT. Recently, the treatment of LACC has been a point of controversy. We have no prospective data to justify that surgery or modern EBRT can be used in place of intracavitary BT boost in women with locally advanced CC. This study aims to review existing information about brachytherapy alternatives after neoadjuvant chemoradiation.

MATERIAL and METHODS

An electronic search of the PubMed database was conducted to obtain key literature for cervical cancers. The MEDLINE/PubMED (www.ncbi.nlm.nih.gov) database was chosen as it remains the most widely used resource for medical literature. Additional records were searched in other resources – EMBASE (www.embase.com), Cochrane Central Register of Controlled Trials (CENTRAL) (www.thecochranelibrary.com), Google Scholar (scholar.google.com/), CINAHL (www.ebscohost.com), APA (www.apa.org/pubs/ databases), Opengrey (http://www.opengrey.eu/); Z-library (https://z-lib.org/); Books; The sameas search strategies was used for all databases.The following search terms were used: “Cervical Cancer”, “Adjuvant hysterectomy”, “IMRT Boost”,“SBRT”.

Inclusion criterias:

I. Studies that included patients with intact locally advanced cervical cancer (> FIGO IB2)
II. Studies that included patients with nonmetastatic cervical cancer
III. Studies that included patients treated with Linac
IV. Studies that included more than 5 patients with investigated intervention
V. Studies that provided at least one primary endpoint, including local control (LC), overall survival (OS), or grade ≥3 toxicity

Exclusion Criterias:

I. Studies that included patients with recurrent cervical cancer
II. Studies that included patients with metastatic cervical cancer
III. Studies that included patients treated with Cyber knife or Tomotherapy
IV. Studies that included less than 5 patients with investigated intervention
V. Studies that provided no primary endpoint, including local control (LC), overall survival (OS), or grade ≥3 toxicity
VI. Studies that included patients with only FIGO IB stage group cervical cancer
VII. Case reports, review articles and editorials.

Human studies published in English were used to narrow down the search results. Duplicate studies were deleted from the studies collected from the databases for each search phrase. Following the first screening of abstracts, full-text publications were evaluated for eligibility in the second screening step. The studies were screened individually for each search term

RESULTS

Applying the predefined inclusion criteria, the first phase of screening identified 18 articles for the first search term (“Adjuvant hysterectomy” AND “Cervical Cancer”), 10 article for the second search term (“IMRT boost” AND Cervical cancer”) and 11 articles for the third search term (“SBRT” AND “Cervical Cancer”). In sum 39 articles were identified to be relevant for the second phase of screening.

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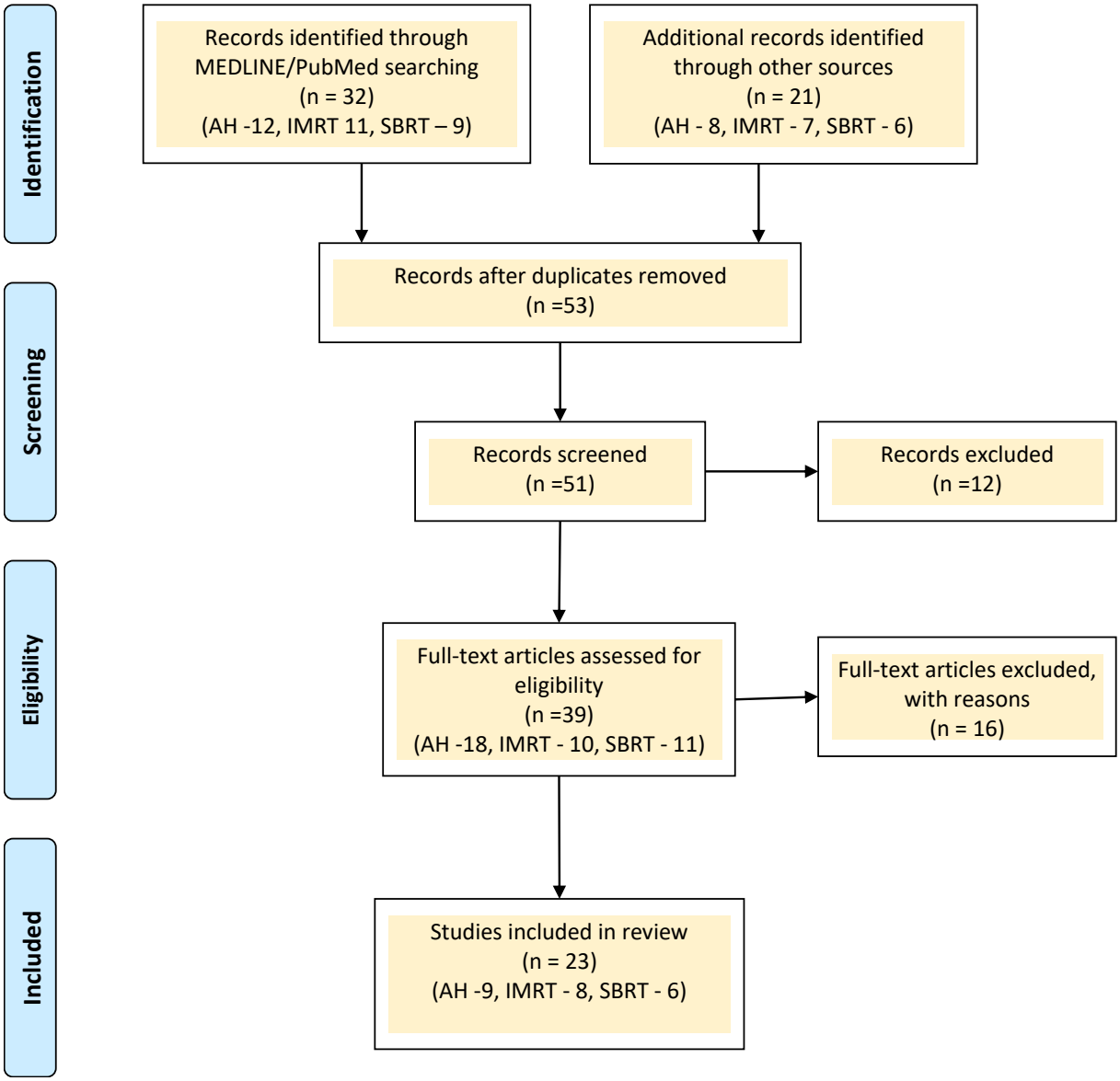

Figure 1. Identification of studies via databases and registers

During the second phase of screening, the full texts of each article were analysed individually. Studies that included less than five patients with investigated intervention or did not provide enough information about at least one primary endpoint were excluded. A total of 20 (11-adjuvant hysterectomy, 4-IMRT boost, 5-SBRT boost) papers met the selection criteria and were found eligible for this review (Fig.1).

Adjuvant hysterectomy

The University of Texas M. D. Anderson Cancer Center first introduced postirradiation hysterectomy to improve the primary lesion's cure rate; however, some patients were also chosen for pretreatment laparotomy and node dissection to improve the cure rate in patients with nodal metastasis. Series of reports were published by the MD Anderson Cancer Center in the 1970s, since then, the role of adjuvant postirradiation extra fascial hysterectomy has been a source of controversy.

The available data have defined neither the potential role post-irradiation hysterectomy nor the extent of radicality that this procedure should require to maximize the outcomes without increasing the level of morbidity. A few authors reported disappointing results related to the high rate of surgical complications while applying hysterectomies after the entire course of chemoradiation, consisting of EBRT combined with chemotherapy followed by intracavitary brachytherapy (7-8).

Previously in 2007, Ferrardina (9) and colleagues demonstrated that neoadjuvant chemoradiotherapy followed by hysterectomy resulted in a high proportion of full pathological response and an acceptable rate of DFS and OS. Furthermore, a low % age of intra- and post-operative complications was observed. This was the first prospective clinical trial to exclude brachytherapy as a part of treatment.

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The authors of this study overlooked the adjuvant hysterectomy (AH) conception in favor of a multimodal strategy that included chemoradiation and radical hysterectomy (RH). Patients who included in the study were FIGO stage IB2-IVA. Results could be criticized as we cannot see outcomes separately for the different stage groups and makes an impression as results could be improved identical for all stage groups.

Shortly thereafter, Francesco Fanfani and colleagues published another study from Italy. The research enrolled 39 patients with stage IIIB CC as defined by the International Federation of Gynecology (FIGO). Patients were treated with whole pelvic irradiation (range, 39.6-50.4 Gy) combined with cisplatin and 5-FU. Between 6 and 8 weeks after the end of neoadjuvant CTRT, patients who responded clinically got a RH. In conclusion, the authors noted that chemoradiation followed by RH may be feasible in patients with stage IIIB cervical cancers with a low rate of complications and a survival outcome comparable to that of chemoradiotherapy, allowing for assessment of pathological response and its impact on clinical outcomes (10).

In 2010, Ferrardina and colleagues published updated paper with a median follow up of 58 months (28 months in the previous report) where 3- and 5-years OS and DFS were still awe-inspiring while consequences resulting from multimodality treatment were reported to be acceptable. According to observations, radical surgery was related with a reduced risk of local recurrence than extra fascial hysterectomy or no surgery. Patients with a large residual tumor who had completion-surgery had a better prognosis. Surprisingly, clinical outcomes were quite encouraging with 5-year DFS and OS of 75% and 70%, respectively; moreover, in stage III–IVA patients, 5-year DFS and OS of 58% and 62% was reported (11). In their next phase II clinical trial (12), published in International Journal of radiation Oncology in 2014, Ferrandina and colleagues aimed to evaluate the efficacy of accelerated fractionation radiation therapy by concomitant boost associated with the whole pelvic chemoradiation in improving the rate of complete pathological response to treatment in patients with FIGO stage IB2-IVA cervical cancer. Patients with stage IIB and III-IVA disease accounted for roughly 76% and 15%, respectively. It is arguable if that kind of stage proportional distribution could influence the results - a high rate of complete pathological response to chemoradiation and a very encouraging local control rate with an acceptable toxicity profile. The study got criticized by H.B. Govardhan, MD, and colleagues from India not only for stage distribution but also because of the total duration of treatment.

L. Cetina published the first prospective randomized controlled phase III clinical study in 2013 (13). Researchers wanted to demonstrate that RH could result in improved outcomes in FIGO stage IB2–IIB cervical cancer when compared with standard intracavitary brachytherapy after identical chemoradiation. To optimize the efficacy of chemoradiation, a combination of gemcitabine and cisplatin was delivered based on the results of a phase II trial where a high Path CR rate of 77.5% and a survival rate >95% was observed at a median follow-up of 20 (6–29) months (14). The results indicated that the three-year PFS and OS were comparable in both groups, as were the proportions of local and systemic failures. The authors proposed that in patients receiving efficacious chemoradiation, RH rather than normal intracavitary brachytherapy did not reduce survival. However, as the study was not a non-inferiority trial, it was unable to demonstrate that RH following concurrent chemoradiation with cisplatin and gemcitabine could improve survival outcomes.

Gallotta and colleagues went above and beyond to reduce surgical complications and improve clinical results by implementing laparoscopic hysterectomy (LH) following chemoradiation. This was the first prospective, phase II clinical trial that looked at the feasibility and post-operative morbidity of radical LH and pelvic + aortic lymph node dissection (PLND) in LACC patients who had received preoperative CCRT (15). The trial enrolled 58 individuals with FIGO Stage IB2-III. OS or DFS were not included as study outcomes. Following chemoradiation, 44.8 % of pathologically complete responses were reported. The study findings indicated that for individuals with LACC who had undergone preoperative chemoradiation laparoscopic RH was the feasible option with peri-operative outcomes comparable to those observed in patients with early-stage CC and LACC receiving neoadjuvant chemotherapy.

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Table 1. Adjuvant Hysterectomy Studies

Study	Study type	N of P.	FIGO stage	Treatment	Comparison	Median Follow up time	Findings		
							OS	DFS	Surgical complications
Ferrandina et al 2007 (9)	Prospective phase II clinical trial	161	IB2-IVA	EBRT in combination with cisplatin and 5-fluorouracil followed by RH	no	28 (3–126 months)	2-year OS 97% and 5-year OS 90%,	2-year DFS 91% and 5-year DFS 83%	Intraoperative – 8,5% Early postoperative G3 – 3,3% G2 – 7.9% Late postoperative – 6.6% ALL G3 – 9,9%
Fanfani et al. 2009 (10)	Retrospective observational descriptive review	39 AH	III B	CCRT followed by AH (median 44.1 Gy; range - 39.6-50.4 Gy) in combination with cisplatin and 5-FU.	no	33 (3 – 80 months)	3-year OS was 70.0%	3-year DFS was 67.6%	G3 – 20% G2 – 48.6 % G1 – 80%
Ferrandina et al 2010 (11)	Prospective phase II clinical trial	174	IB - IVA	CCRT (39,6 – 50,4 Gy combined with cisplatin (20 mg/m2, 2-h intravenous infusion) and 5-FU (1,000 mg/m2, 24-h continuous intravenous infusion) (both on days 1–4 and days 27–30)	no	58 (3–168 months)	e 3-year and 5-year OS were 82.5% and 77.4%	3-year and 5-year DFS were 77.0% and 75.5% ,	Intraoperative only G1 – 8% Early postoperative G3/4 – 3.4% G1/2 – 16.6% Late postoperative G4 – 1,16% G3 – 3,4 % G1/2 – 8%
Cetina et al 2013 (13)	Prospective randomized controlled phase III clinical trial	211 (AH 111pt and BCT 110pt)	I B2 – II B	CCRT 50,4 Gy concurrently with six courses of cisplatin at 40 mg/m2 and gemcitabine at 125 mg/m2 per week	Brachy therapy	36 (3 – 80 months)	3-years OS was 74.5% vs 76.3%	3-year DFS was 71.7% vs 74.8%	NA
Ferrandina et al 2014 (12)	Prospective phase II clinical trial	103	I B2-IV A	CCRT followed by AH (39,6 Gy to pelvis + 10,8 Gy boost to primary tumor and Parametria) in combination with cisplatin (20 mg/m2, 2-h IV, on days 1-4 and 26-30 of treatment) and capecitabine (1300 mg/m2/daily, orally) during the first 2 and last 2 weeks of treatment.	no	36 (7 – 85 months)	3-years OS was 86.1%	3-year DFS was 73 %	All – 25% G3 – 3% G2 – 8% G1 – 13%
Rem et al 2014 (16)	Retrospective observational descriptive review	43	IB - IIB	CCRT followed by AH (40 to 46 Gy in 20 to 23 fractions and concurrent weekly low-dose cisplatin in a dose of 40mg/m2) plus vaginal cuff brachytherapy after surgery	no	29 months	5-years OS 85.5%	5-years DFS 82.1%	G3 – 6,9 % (3pt) G2 – 60,4% (26pt) G1 – 37,2% (16pt)
Gallotta et al 2015 (15)	Prospective phase II clinical trial	58	IB - III	CCRT followed by AH (total dose of 45-50,4 Gy combined with cisplatin and 5-fluorouracil)	no	22 (5-50 months)	NA	NA	All – 40% G3 – 7.25% G2 – 14.5% G1 – 18.25%
Haas et al 2017 (17)	Retrospective observational descriptive review	248 (87 AH and 161 BCT)	IB1 - IVA	CCRT followed by laparoscopic AH or brachytherapy (EBRT median dose of 50,4 Gy combined with 20 mg/m2 cisplatin and 1000mg 5-FU (/m2 KOF) on days 1–5 in the 1st and 5th week of treatment	Brachy therapy		5-years OS (with and without residual after CCRT) 41-80% vs 76,9 -82%	5-years DFS 73,9 – 75% vs 84.6-100%	NA
Yoshida et al 2019 (18)	Retrospective observational descriptive review	136 (AH 50pt and 76pt BCT)	IB2-IIB	CCRT followed by AH ot intracavitary brachytherapy (EBRT 50.4Gy in combination with two course of chemotherapy - cisplatin (70 mg/m2 on day 1) and 5-fluorouracil (700 mg/m2, 24 h continuous intravenous infusion on days 1–4)	Brachy therapy	64.8 (range 4.8 – 143.9 months)	5-year OS 87.7% vs 66.2%	5-year DFS 78.3% vs 56.9%	G3 – 23,1% G ½ - 32.9% No adverse events in 44%

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Notably, none of the previous studies proved that RH could enhance outcomes with decreased toxicity. Therefore, the use of RH has been questioned, and the simple hysterectomy (Piver I) after chemoradiation has been considered an alternative by Haas and colleagues (17).

They retrospectively analyzed the cancer registry of Saxony-Anhalt, a federal state of Germany. Reports of 248 patients were eligible for analysis from which 161 received brachytherapy, and 87 underwent a simple hysterectomy. The researchers discovered that the reaction to chemoradiation has an effect on the result. For patients with clinically no residual tumor the estimated 5-year DFS rate was 100% in the control group and 73.9 % in the surgical group (p = 0.103), while it was 75.0 and 84.6 % in the group of patients with residual lesions, respectively (p = 0.028). The 5-year DOS rate for patients with residual tumor was 41.7 and 76.9 %, respectively, in groups 1 and 2. This difference was statistically significant (Fig. 3b; p = 0.011).

Furthermore, the estimated DOS for patients without residual tumor was also similar in group 1 and group 2 and was estimated to be 80.0 and 82.0%, whilst in individuals with the residual tumor, it was 41.7 and 76.9% in group 1 and 2, respectively. Importantly, this difference was statistically significant (p = 0.011). The authors concluded that sample hysterectomy following chemoradiation without brachytherapy is feasible in selected patients and that the survival benefit of hysterectomy in patients with residual illness following RCT should be validated in prospective randomized trials.

Yoshida and colleagues (18) recently published a study comparing the outcomes of neoadjuvant concurrent chemotherapy and radiation followed by RH and PLND in contrast with definitive chemoradiation using inverse probability of treatment weighting (IPTW). While the Kaplan–Meier curves for PFS and OS did not differ significantly across groups (p = 0.219 and 0.217, respectively), the Kaplan–Meier curves for IPTW adjusted PFS and OS were considerably longer in the NACRT group than in the CRT group (p = 0.027 and p = 0.017, respectively). In the NACRT and CRT groups, IPTW adjusted 5-year DFS rates were 78.3% and 56.9%, and IPTW adjusted 5-year OS rates were 87.7% and 66.2%, respectively. Surprisingly study suggested that surgery after CRT reduced pelvic recurrence and, as a result, provided favourable PFS and OS.

3DCRT and IMRT Boost - technique matters

First papers about treating cervical cancer with EBRT alone appeared in the early 1960s. All the papers were fragmented, had shorter follow up periods and all the results were not summarized as conclusions. Castro et al. conducted a retrospective analysis of 108 patients treated with EBRT alone in 1970, concluding that 50 Gy was insufficient for cervical cancer control and that a 20 Gy boost was required (19). In 1983 Ulmer reported they had similar results with EBRT alone in comparison to combined intracavitary and EBRT (5-years OS by stages: II – 75 %, III – 30%, IV – 13%) (20). They obtained homogeneous dose distribution with plan parameter alterations. Radiation-induced side effects were observed in most of the patients and also similar to somewhat reported before with combined treatment. There was no toxicity in the G4 to 5 ranges. Notably, all 150 patients had poor prognoses - they were older, had locally advanced disease, and had poor performance status. Soon after, In 1986 Montana studied survival rates and the relationship between complications and point A doses for stage III CC (21). Eighty-eight patients were treated with EBRT alone in that trial, out of 203. Results showed that 2 years DFS was more desirable for the combination therapy group, but this difference was not maintained exceeding 5 years.

The article, published by Lisa Helen Barraclough in the International Journal of Radiation Oncology Biology and Physics in 2008, reported the results of the retrospective observational descriptive review (22). The study included 44 patients treated with EBRT boost. A total dose of 60–65 Gy was given to 31 patients (71%). Two patients received 67.5–70 Gy, 11 patients received 54–58 Gy. During a median follow-up of 28 months (range, 3–96 months), 2-year OS was reported to be 64 %% and 5-year OS to be 49.3 %, while treatment-related toxicity was relatively tolerable – G3 – 2%, G2 – 16 %, and G1 – 22.5 %. According to our present knowledge, the results could be disputed because the research population has only received concurrent treatment since 2001. A dose of 40 mg/m2 with a maximum of 70 mg is given weekly during radiotherapy as long as the treatment is tolerated. From 44 patients, chemotherapy was administered to 19 patients (43%) - neoadjuvantly to 11 patients and concurrently to 8. However, this study demonstrates that an EBRT boost could be a reasonable option when brachytherapy boost cannot be performed.

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Table 2. 3DCRT and IMRT Boost

Study	Study type	N of P.	FIGO stage	Chemo	RT technique	Dose	Comparison	Median Follow up time	Findings		
									OS	DFS	Toxicity
Barraclough et al 2008 (22)	Retrospective observational descriptive review	44	IB-IVA	Cisplatin	3DCRT	phase 1 volume was 40–45 Gy in 20 fractions over 26 days. A dose of 15–25 Gy is given in 8–10 fractions given over 10–12 days for phase 2	no	28 (3–96 months)	2-year OS 64% and 5-year OS 49.3%,	NA	G3 – 2% G2 – 16% G1 – 22.5%
Park et al 2010 (23)	Prospective clinical trial	9	IIA-IIIB	Cisplatin	3DCRT	whole pelvis RT with a median dose of 50 Gy (range, 40-50 Gy) before the boost. The median dose of the boost was 30 Gy (range, 25-30 Gy).	no	17.6 (4.9-27.3 months)	NA	2-year DFS 52%	G3 – NO G2 – 22% G1 – 55.5%
Matsuura et al 2012 (24)	Prospective clinical trial	16	IIB-IVA	NA	3DCRT	The median total dose was 66 Gy (range: 66–73 Gy) on the CCB The median total dose was 60 Gy (range: 60–66.2 Gy) on the CF schedule.	No (different fractionations were compared CF vs CCB)	40 months (range: 6–93 months)	3-years OS 43,8%	NA	G3 – NO G2 – 25% G1 – 43%
Kadkhodayan et al 2013 (25)	Prospective clinical trial	30	IIB-IIIB	Cisplatin 35 mg/m2 weekly	3DCRT	50 Gy within 5 weeks to whole pelvic that has followed by a localized boost dose on tumor to 70 Gy	No	25.5 months (rang: 11-56 months)	3-years OS 39.1% (±9%)	NA	**G4-** Diarrhea 6.6% **G3-** Neutropenia 13.3%, Diarrhea 6.66% **G2**–Anemia 23%, neutropenia 33.3%, Nausea and vomiting 10%, Diarrhea 3% **G1** – Anemia 33%, Neutropenia 30%, Nausea and vomiting 3.33%, Diarrhea 6.66%
Mazzola et al 2016 (26)	Prospective clinical trial	30	II-III	Cisplatin 40 mg/mq	SIB - VMAT	EBRT - 66 Gy to the macroscopic disease and 54 Gy to the pelvic nodes in 30 fractions	no	32 (8-48 months).	**3-years OS 93%**	NA	G3 – NO G2 – $3% G1 – 63%
Kim et al 2017 (27)	Multicenter Retrospective Study	75	I-IV	NA	3D-CRT 24pt (32%) IMRT 51pt (68%)	46 Gy (range, 40-54 Gy) for whole pelvis and 24 Gy (range, 9-35 Gy) for Boost	no	33 months (range, 2-104 months)	5-years OS 75%	5-years DFS 54.7%	G3 – 12% G1/2 - NA
Delgado et al 2019 (28)	Retrospective observational descriptive review	92 (55 EBRT and 37 ICB)	IB1-IVA	Cisplatin	3DCRT	pelvic 3D conformal EBRT (range, 45-50.4 Gy) and 3D conformal EBRT boost (16.2 Gy)	ICB	67 months (range: 5-144 months)	**5-years OS 58% (EBRT) vs. 82% (ICB);**	**5-years DFS 38% (EBRT) vs. 79% (ICB);**	NA
Lazzari et al 2020 (29)	Retrospective observational descriptive review	25	IIB-IVB	18 (72%) patients received weekly cisplatin, seven (28%) cisplatin and paclitaxel	IMRT	EBRT of 45–50.4 Gy in 25–28 fractions (1.8 Gy/fraction) to pelvis ±para-aortic lymph nodes and sequential IMRT boost	no	26months (range:4 – 77 months)	2-year OS 67%	2-year DFS 55%	G3/4 – NO Acute G2 – 12 % G1 – 28% Late G2 – 12% G1 – 21%

Few prospective clinical trials (23-25) tried to determine the clinical outcomes and feasibility of EBRT for locally advanced cervical cancer when patients were unable to receive an intracavitary brachytherapy boost. Although the results of 3DCRT-EBRT were poor and had never been comparable to the results of brachytherapy, EBRT was still considered a promising and feasible modality as an alternative radical therapy in cases where ICBT could not be administered. Mazzola and colleagues reported the first prospective clinical trial when the VMAT technique was used instead of 3DCRT techniques in 2016 (26). By the time, there have been no reports of intensity-modulated radiotherapy used to boost the central pelvis in place of brachytherapy and notably, there was a need of new clinical trials evaluating potential role of IMRT boost in cervical cancer treatment. After the first introduction in clinical practice, IMRT was considered to have considerable potential in treating women with gynecologic malignancies. Initial clinical experience showed that IMRT resulted in less acute and chronic gastrointestinal toxicity and spared the pelvic bone marrow, reducing the risk of hematologic toxicity. Soon after, IMRT was considered to be a dose-escalation method instead of brachytherapy. Numerous authors reported promising data about IMRT plane evaluation, dosimetry, and toxicity. Not surprisingly, the results reported by Mazzola et al. were completely different from the previously published data. During a median follow-up of 32 months, the 3-years OS was 93%. The absence of pelvic nodal recurrences suggested that a higher dose to the PET-positive nodes employing the SIB approach could be an effective strategy. Although the data were preliminary, these results seemed unexpected compared to what was suggested in the literature: In the treatment of cervical cancer, the LC rates are related to the biologically equivalent dose: high doses (80-95 Gy to the primary tumor) administered over a short time (inferior to 50-55 days) has significant impact on LC and OS. There is a need for long term results and update of this study, which may provide us with a much more interesting data.

Delgado et al. (2019) published the first retrospective study comparing the results of EBRT boost versus brachytherapy boost (28). But the RT technique applied in the study was 3DCRT vs. intracavitary BT. The 5-year OS rate in the BT-IC group (82 %) was greater than in the EBRT group, as expected (68 %). However, when compared to other published studies, the outcomes of 3DCRT were still superior. The dominance of the lower FIGO stage (IIB) and the retrospective aspect of the study could be the main grounds for criticism, which could lead to better outcomes for 3DCRT than previous published series. Lazzari published a study in the International Journal of Gynecological Cancer in 2020 regarding the clinical outcomes of IMRT in locally advanced cervical cancer in the absence of BT (29). Three main facts were highlighted: Six months after the IMRT boost, 22 (88 %) of the 25 patients had complete local control of the cervix; For all stages, the 2-year OS, DFS, and local control (LC) rates were 67 %, 55 %, and 78 %, respectively; Following the delivery of an IMRT boost, no G3-4 toxicities were noted (Table 2).

SBRT boost

Briefly, reviewing historical aspects of SRS/SBRT, during the late 1980s and early 1990s, SRS grew rapidly. The main indications for this kind of treatment were pain syndromes or movement disorders. Sturm et al. were one of the first authors reporting brain metastasis as an indication for SRS in 1987. SBRT developed about a decade later than SRS but was based on similar principles. In Karolinska Hospital Stockholm, SRS procedures were well utilized. Ingmar Lax and radiation oncologist Henric Blomgren reasoned that similar local control outcomes could be achieved at different body sites with one or a few focally delivered fractions, even if targeting and immobilization issues for sites outside of brain were more much difficult. Lax and Blomgren described their technique in 1994 (30) and in 1995 reported clinical outcomes in 31 patients with 42 malignant tumors located in the liver, lung, or retroperitoneum. They achieved local control in 80 % of cases. David Larson visited the Karolinska Hospital in 1993 as an observer. He brought Lax and Blomgren's technique back to his home institution, where he treated 150 patients during 1993–1995. New treatment delivery techniques (i.e., dynamic-arc treatment and intensity-modulated radiotherapy [IMRT]) and availability of highly accurate immobilization and repositioning systems made SBRT possible to relatively small pelvic tumors. Optimal repositioning with fiducial markers and an inflatable rectal probe had been reported for prostate cancer patients in the early 2000s.

All mentioned above made a basement for future research of using SBRT for cervical cancer and became an inspiration for several studies and clinical trials investigating the efficacy and toxicity of SBRT for cervical cancer and its impact on survival. Although there are no randomized controlled trials evaluating its effectiveness of toxicity, SBRT has been adopted as one of the treatment options for recurrent, oligometastatic, and sometimes in up-front settings for gynecologic tumors, alone or with EBRT. Several retrospective clinical reports and retrospective dosimetric reports have shown that SBRT appears to be a reasonable treatment option for patients unable to receive intracavitary treatment.

Haas et al. (31) and Marnitz et al. (33) used the Cyberknife to track the previously implanted gold fiducials in the cervix for precise SBRT boost delivery resulting in a high rate of local control (both 100%).

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Haas and colleagues reported no G3 or higher toxicity, while Marnitz and colleagues reported a high rate of treatment-related toxicity. Because of the shorter median follow-up time (only 14 months for Haas et al. and six months for Marnitz et al.), there is no information reported about late toxicity, 3- or 5-years OS or DFS. Hsieh et al. reported the 3-year OS 46.9% and the 3-years DFS 77.8% but also accounted for a longer overall treatment time (median = 79 days) and included patients with advanced disease. One patient presented with grade 3 diarrhea, and another had grade 3 thrombocytopenia during treatment.

The study had several limitations: no statistical conclusions can be drawn due to a small number of cases, the retrospective study design, a short follow-up period, so long-term results and close monitoring are further required, not all the patients had implanted fiducial markers, so the radiotherapy margin could not be reduced effectively, even with image-guided technique, which could be the main reason for late G2 rectal toxicity (33,3%, 3/9pt) in the study.

Table 3. SBRT Boost

Study	Study type	N of P.	FIGO stage	Machine	Treatment	Comparison	Median Follow up time	Findings		
								OS	DFS	Toxicity
Haas et al 2012 (31)	Retrospective chart review	6	NA	Cyber knife	whole pelvis RT 45–50.4 Gy in 1.8 Gy/fraction followed by **SBRT boost (20Gy/5fx or 19.5/3fx)**	no	14 months	NA	1-year DFS 100%	G3/4 – NO G2 – NA G1 – 66% (4/6 pt)
Hsieh et al 2013 (32)	Retrospective observational descriptive review	9	IIB to IVA	Tomotherapy	WPRT followed by **SBRT (27-16 Gy/5–9 fractions)**	no	13 months (range: 4–40 months)	3-year OS 46.9%	3-years DFS 77.8%	**G3** -Diarrhea 11% cytopenia – 11% **G2** -Diarrhea – 11%, GU – 11%, cytopenia – 22% **G1** – Nausea 100%, Diarrhea - 78%, GU – 89%, cytopenia – 89%
Marnits et al 2013 (33)	Retrospective observational descriptive review	11	IIB-IIIB	Cyber Knife	WPRT of 50.4Gy with SIB to parametrium 59.36Gy followed by **SBRT (30Gy/5 fractions)**	no	6 months	NA	NA	**G4 –** cytopenia – 9% **G3** – cytopenia 27%, **G2** – Cytopenia - 63%, GU – 18%, GI-18% **G1** – cytopenia - 36%, GU – 81%, GI – 81%, vaginal-100%
Mantz et al 2015 (34)	Prospective clinical trial	40	NA	NA	WPRT 45Gy follow by **SBRT (40Gy/ 5fx delivered over a 10-day)**	no	51 months	NA	2-years DFS 77.5%	**NA**
O'donnell et al 2018 (35)	Retrospective database review	**15,905** 14,394 (90.5%) brachytherapy **42 (0.8%) SBRT** 1468 (9.2%) IMRT	I-IVB	NA	WPRT followed by boost – ICB vs IMRT vs SBRT	ICB vs IMRT	NA	**Median OS ICB 99.1 Months, SBRT - 30.6 months,** IMRT - 29.8 months. **With Propensity-Matched Analysis 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 = 0.746Y2.926, P = 0.263).**		
Albuquerqe et al 2020 (36)	A Phase II Trial	15	IB2-IVB	NA	whole-pelvis radiotherapy (45 Gy in 25 fractions with SIB to positive nodes) followed by **SBRT (28 Gy/4 fractions)**	no	19 months	2 years OS 53.3%	2 years DFS 46.7%	**G3/4 - 26.7% Study was closed early due to toxicity concerns.**

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In 2019, O'Donnell et al. (35) published the results of a database evaluation of 15,905 women with CC, of whom 14,394 (90.5%) underwent brachytherapy, 42 (0.8%) received SBRT, and 1468 (9.2%) received IMRT. Patients who received brachytherapy as a boost survived on average 99.1 months, those who received SBRT as a boost survived on average 30.6 months, and those who received IMRT as a boost survived on average 29.8 months. There was no significant difference in overall survival between those who received SBRT boost and those who received brachytherapy boost using Propensity-Matched Analysis. Multivariable analysis identified the following factors as being significantly associated with decreased overall survival: increasing age, insurance, histology of adenocarcinoma, progression of the disease's FIGO stage, pelvic nodal involvement, presence of distant metastasis, and receiving IMRT rather than brachytherapy.

The latest clinical trial reported by Albuquerque et al. (36) in 2020, was discontinued early due to toxicity concerns (G3/4 toxicity- 26.7%). Fifteen patients were treated with whole-pelvis radiation (45 Gy in 25 fractions with SIB to positive nodes), followed by SBRT boost (28 Gy/4 fractions) in 15 patients. The local control rate was 70%, which is equivalent to the lower range for standard therapy in patients with similarly advanced stage and bulky disease, where the local control rate ranges from 75-85 %, but lower than reported in previous SBRT studies. A significant number of participants developed regional and systemic recurrences related to the high number of bulky advanced-stage tumors. These systemic failures with significant co-morbidities were a significant driver of patient mortality in this trial (Table 3).

DISCUSSION

Since chemoradiation was established, the prognosis of patients with LACC has improved. However, some patients still develop treatment-resistant tumors and have a poor prognosis. During this review, a huge gap in the literature was noted about alternatives to brachytherapy. There are no prospective randomized controlled trials with enough sample size evaluating efficacy or toxicity for different approaches compared to brachytherapy. Most studies have a very small sample size, short follow-up times and most were retrospectives in nature. Radiation therapy dosing regimens and fractionations varied widely from one study to the other, as well as techniques of hysterectomy. Studies also used different parameters of survival and toxicity, making it difficult to perform across-studies comparisons and dose-toxicity evaluation. Theoretically, SBRT is the most certain technique among all EBRT modalities in terms of its ability to simulate a BT dose distribution with a steep dose gradient and, as a result, achieve the same treatment outcomes as ICB, at least theoretically. SBRT allows for the delivery of high-dose chemotherapy directly to the tumor while conserving as much healthy tissue as is reasonably practicable. SBRT has been shown to be superior in a few dosimetric experiments due to its great target coverage and OAR sparing properties. But whether an extremely high dose within the tumor is required radiobiologically remains a matter of debate and will not be discussed in detail in this paper. Although the BT profile (characterized by an exceptionally high dose within the applicators) is exceedingly effective, it cannot match with the homogeneity of the EBRT dose throughout the target volume.

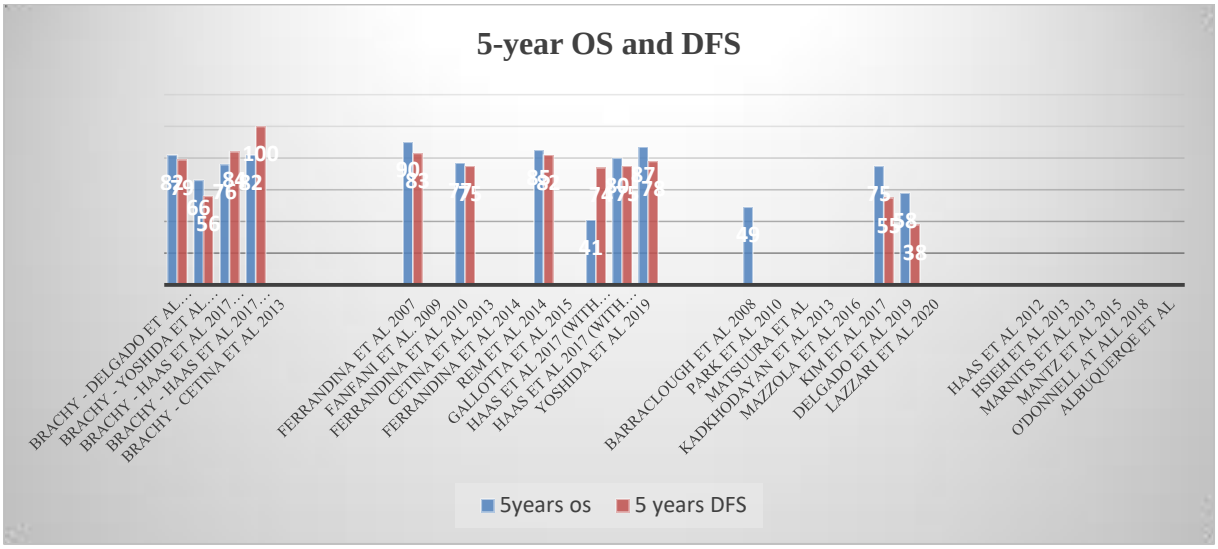

Figure 2. 5-years OS and DFS

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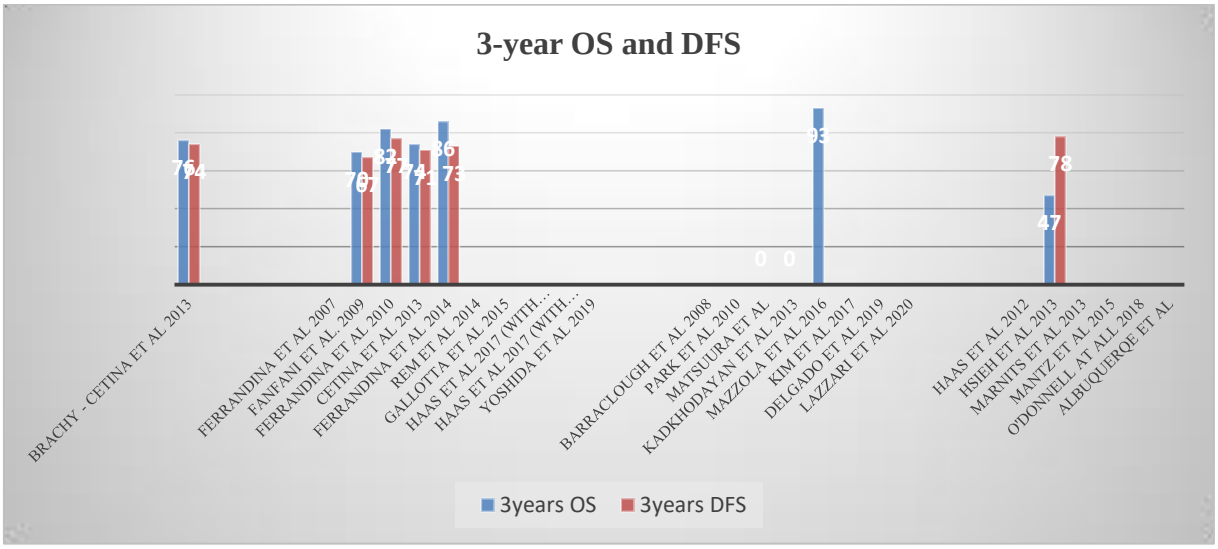

Figure 3. 3-years OS and DFS

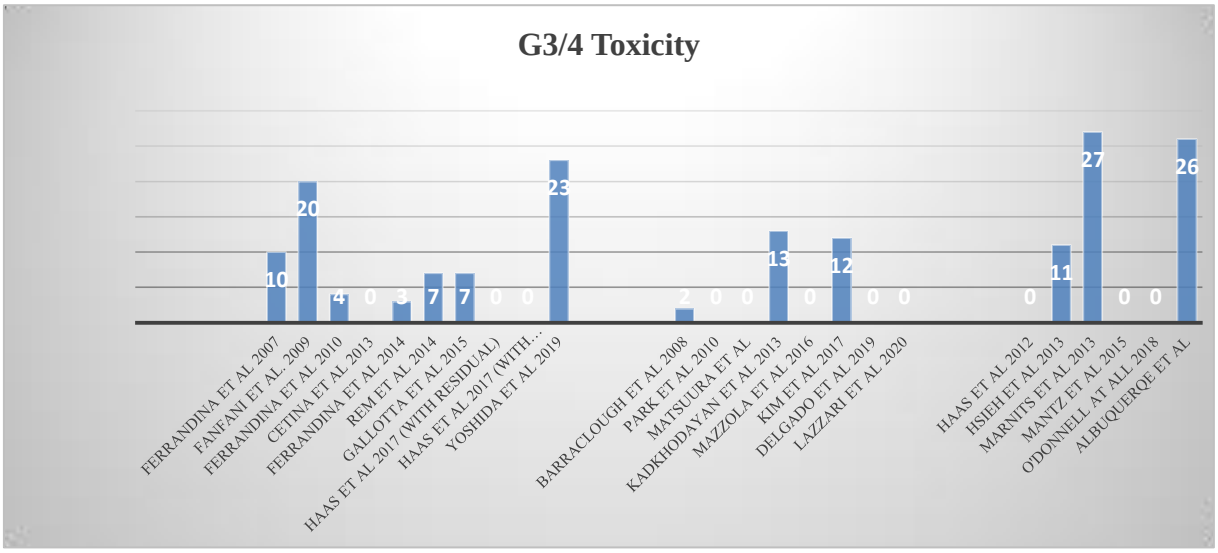

Figure 4. G3/4 Toxicity.

If we look to our results from the standpoint of 5-years OS and DFS (Fig. 2), notably, there is a look of date for EBRT techniques; we have no date about SBRT. Unlikely to EBRT/SBRT, we have more data for AH. Median 5-years OS and DFS after AH was 76.6% (range: 41%-90%) and 77,8% (range: 74%-83%). Median 5-years OS and DFS after EBRT (3DCRT - 187pt/IMRT 24pt) 59.9% (range: 49%-75%) and 46.5% (range: 38%-55%). We have no 5-years data for the SBRT boost.

In terms of 3-years OS adjuvant hysterectomy provides the same results as brachytherapy 78% (range 70%-86%) vs. 76%, while EBRT 3-years OS is 58.6% (range: 39.1%-93%) and 46% for SBRT (Fig.3). There is only one study reporting 30years DFS after SBRT (Hsieh et al. 2013) – 78%, which seems quite promising. As for toxicity, SBRT is associated with more treatment-related toxicity (Fig.4.); however, reported as acceptably by most authors.

Rate of G3 toxicity for hysterectomy, EBRT and SBRT were 10.5% (range: 3%-23%), 3,8% (range:0-13%) and 16% (range: 0-27%) respectively.

CONCLUSION

When all these alternative approaches to ICB are evaluated, adjuvant hysterectomy appears to have treatment outcomes comparable to standard of care, while SBRT appears to have only modest yearly results at the moment. As a result, the majority of writers believe that neoadjuvant chemoradiation followed by radical surgery or SBRT may be a realistic therapeutic option for patients with LACC, not merely when ICB is unavailable, technically impractical, or rejected. Large prospective randomized controlled trials are required to conclusively demonstrate or invalidate non-ICB alternatives for cervical cancer treatment.

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