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SYSTEMATIC REVIEW

Salvage surgery for patients with residual disease after chemoradiation therapy for locally advanced cervical cancer: A systematic review on indication, complications, and survival

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Abstract

Introduction: Standard treatment for locally advanced cervical cancer is chemoradiation therapy. Treatment with chemoradiation therapy harbors a risk of local residual disease, which can be curatively treated with salvage surgery, but the risk of complications following surgical procedures in radiated tissue is not negligible. The presence of residual disease can be radiologically and/or histologically diagnosed. The objective of this study is to describe studies that report on salvage surgery for patients with locally advanced cervical cancer after primary treatment with chemoradiation therapy. Therefore, we assessed the method of determining the presence of residual disease, the risk of complications, and the survival rate after salvage surgery.

Material and methods: PubMed, EMBASE, and the Cochrane database were searched from inception up to 6 March 2020. Titles and abstracts were independently assessed by two researchers. Studies were eligible for inclusion when patients had locally advanced cervical cancer with radiologically suspected or histologically confirmed residual disease after chemoradiation therapy, diagnosed with a CT, MRI, or PET-CT scan, or biopsy. Information on complications after salvage surgery and survival outcomes had to be reported. Methodological quality of the articles was independently assessed by two researchers with the Newcastle-Ottawa scale.

Results: Of the 2963 screened articles, six studies were included, representing 220 women. A total of 175 patients were treated with salvage surgery, of whom 27%-100% had residual disease on the surgery specimen. Of the 161 patients treated with salvage surgery based on positive biopsy results, 72%-100% showed residual disease on the surgery specimen. Of the 44 patients treated with salvage surgery based on suspected residual disease on radiology, 27%-48% showed residual disease on the salvage surgery specimen. A total of 105 complications were registered in 175

Abbreviations: CRT, chemoradiation therapy; CT, computed tomography; FIGO, International Federation of Gynecology and Obstetrics; LACC, locally advanced cervical cancer; MRI, magnetic resonance imaging; PET, positron emission tomography.

patients treated with salvage surgery. The overall survival rate after salvage surgery was 69% (mean follow-up period of 24.9 months).

Conclusions: It is necessary to confirm residual disease by biopsy before performing salvage surgery in patients with locally advanced cervical cancer primarily treated with chemoradiation therapy. Salvage surgery only based on radiologically suspected residual disease should be avoided to prevent unnecessary surgery and complications.

KEYWORDS

chemoradiation therapy, complications, locally advanced cervical cancer, recurrence, residual disease, salvage surgery, survival

1 | INTRODUCTION

An estimated 570 000 women were diagnosed with cervical cancer in 2018, and globally there were 311 000 registered cervical cancer deaths. Cervical cancer represents 6.6% of all female malignancies worldwide, and is the fourth most common malignancy in women.[1,2] According to the International Federation of Gynecology and Obstetrics (FIGO) staging system 2018, stages IIB-IVA are classified as locally advanced cervical cancer (LACC).[3] In high-income countries, approximately 30%-40% of the patients with cervical cancer have LACC at initial diagnosis.[4]

The standard treatment for LACC is concurrent chemoradiation therapy (CRT), which generally consists of cisplatin-based chemotherapy and external-beam radiotherapy, followed by brachytherapy. CRT improves local control and reduces the risk of local regional recurrence in comparison with radiation therapy alone.[5-9] The 5-year overall survival for patients with LACC ranges from 66% for patients with stage IIB, 40% for Stage III to 22% for stage IVa according to the 26th FIGO annual report.[10] In some medical centers, adjuvant surgery is performed after CRT because of a high recurrence rate, up to 40.2%, after CRT.[11,12] However, adjuvant surgery after CRT is not proven to be effective in improving survival outcomes in patients with LACC,[13,14] and authors conclude that routine use of adjuvant hysterectomy should be avoided because of the morbidity of adjuvant surgery after CRT.[14] In other medical centers, a diagnostic procedure with a biopsy, and/or imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT), or positron emission tomography (PET)-CT scans is performed to assess the presence of residual disease after CRT. Central pelvic residual disease in the absence of metastatic disease can be treated with salvage surgery, such as radical hysterectomy or pelvic exenteration. However, salvage surgery, as well as adjuvant surgery, after CRT is associated with a high risk of postoperative complications due to the effects of radiation-induced tissue damage.[15] Common complications after salvage surgery are fistulas, gastrointestinal or urinary tract complications, and sexual dysfunction. This treatment-related morbidity can decrease the quality of life of patients and influence the survival of patients with cervical cancer.[16-19]

Key message

Residual disease should be histologically confirmed by biopsy before performing salvage surgery in patients with locally advanced cervical cancer treated with chemoradiation therapy to prevent unnecessary surgery and unnecessary complications.

The objective of this study was to describe studies that report on salvage surgery for patients with LACC after primary treatment with CRT. Therefore, we assessed the method of determining the presence of residual disease, the risk of complications, and the survival rate after salvage surgery.

2 | MATERIAL AND METHODS

2.1 | Data sources

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[20] In this systematic review, salvage surgery was defined as surgery after radiologically suspected or histologically confirmed residual disease after primary treatment with CRT. The PubMed, EMBASE, and Cochrane library were searched for articles published from inception up to 6 March 2020 (Table S1). The search query combined synonyms for cervix uteri, uterine cervical neoplasm, chemoradiation therapy and salvage surgery and included MeSH terms. Duplicate articles were manually filtered using the bibliographic database Endnote X9.

2.2 | Eligibility criteria

All titles and abstracts were independently assessed by two researchers (KvK and RE), and any discrepancies between the two reviewers were resolved by a third researcher (TV). The selection

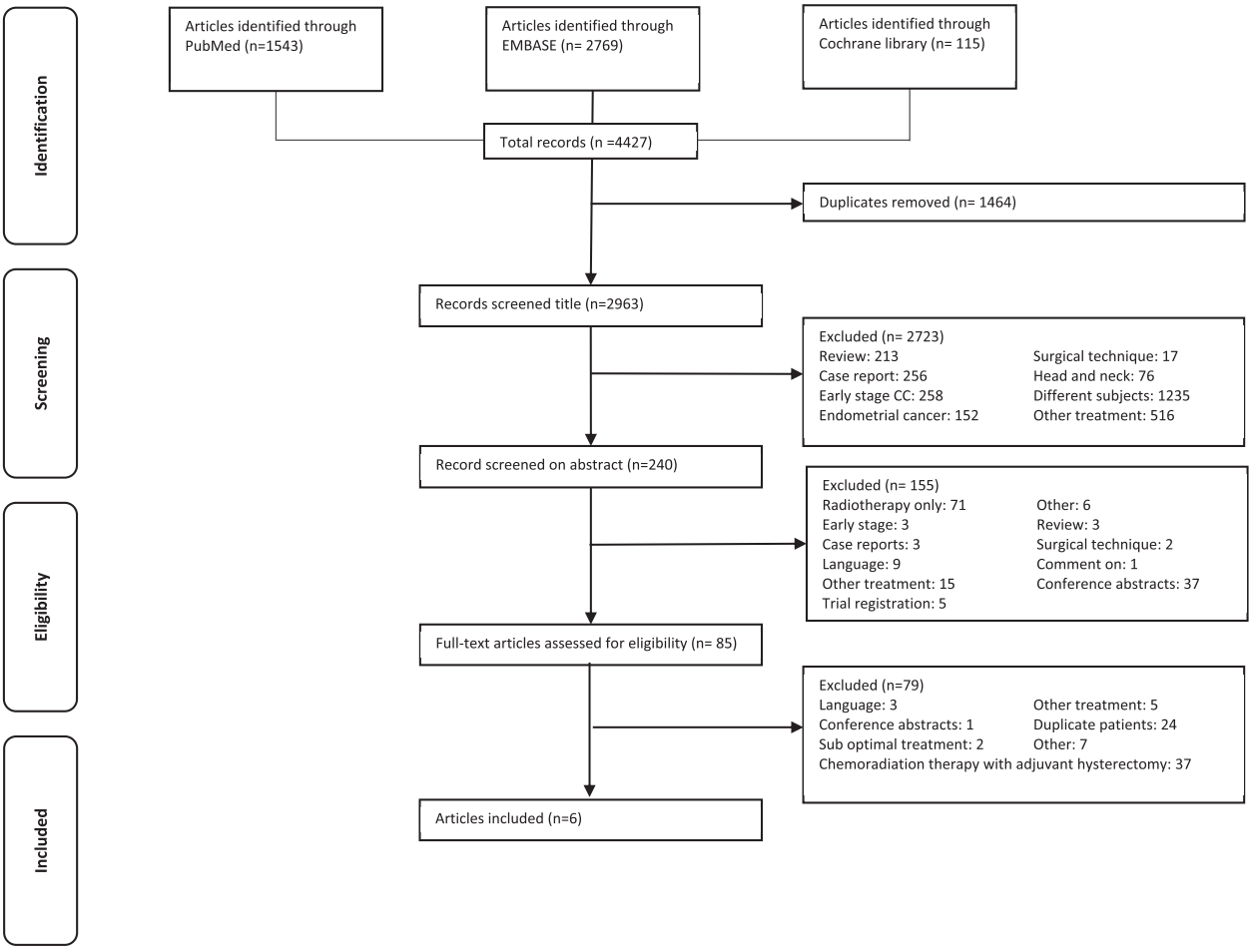

FIGURE 1 Flowchart of the selection procedure for systematic review

of articles was assessed for full text and language was restricted to English. Patients with LACC were suitable for inclusion. Studies were eligible for inclusion when patients had radiologically suspected or histologically residual disease after CRT therapy, diagnosed with a CT, MRI, or PET-CT scan, or biopsy. Information on the complications after salvage surgery, and survival outcomes had to be reported.

Reviews of literature, case reports, and case series with five patients or fewer and letters to the editor were excluded. Articles describing directly planned adjuvant hysterectomy after CRT, without a diagnostic procedure to indicate residual disease, were excluded. Reference lists of all included articles were analyzed in search of missed articles. For studies with duplicate patient information and studies updating previous published series, the most recent data were used.

2.3 | Data collection

From the relevant articles, the following information was extracted: country of study, number of patients with suspected residual disease, number of patients with salvage surgery, stage, histological subtype, dose and regimen of CRT, diagnostic procedure to indicate residual disease, type of salvage surgery, pathology result after salvage surgery, complications after salvage surgery, recurrences, and the overall survival rate. The reported complications in the studies were subdivided into the categories: fistulas, urinary tract, gastrointestinal, infection, and other complications. The complication rates were calculated by dividing the number of complications per category by the total number of patients with salvage surgery. The overall survival rate and recurrence rate in this review were calculated from the total reported number of deaths (or recurrences) in the articles in relation to the patients treated with salvage surgery.

2.4 | Assessment of risk of bias

Two reviewers independently (KvK and RE) determined the quality of the included articles according to the Newcastle-Ottawa Scale for cohort studies.

3 | RESULTS

3.1 | General characteristics of studies

The search revealed 2963 articles after systematically removing duplicates. After screening titles and abstracts, 85 studies were evaluated for full text. After reading the full text, 79 studies did not fulfill the selection criteria. Studies were excluded because

patients were treated with adjuvant hysterectomy (n = 37) or studies appeared to have duplicate patients (n = 24); eighteen studies were excluded for other reasons. Six studies were included in this systematic review, including 220 patients. No additional studies were identified by checking the reference lists. Figure 1 shows the flowchart of the selection process. The six included articles consisted of four retrospective cohort studies and two prospective cohort studies. Of the included studies, two included patients based on radiologically suspected residual disease,[21,22] the others included patients based on histologically confirmed residual disease.[7,21-23] Results of the studies are summarized in Table 1. All studies were assessed as good or fair quality according to the Newcastle-Ottawa Scale for cohort studies (Table 2).[24]

3.2 | Synthesis of the results

In six studies, a total of 220 patients had suspected residual disease after CRT, and salvage surgery was performed in 175 patients (79.6%). In these studies, a total of 45 patients were not treated with salvage surgery, 28 patients because of distant metastases, 13 patients had inoperable tumors, two patients because of histological subtype (small-cell carcinoma and neuroendocrine tumor), one patient refused salvage surgery, and one patient had salvage surgery in another hospital. For three studies, including 79 patients, the time until salvage surgery after completing CRT was known. In the first study, time until surgery was a median of 49 days (range 42-64 days), in the second study it was a median of 76 days (range 56-84 days), and the third study performed salvage surgery between 14 and 18 weeks after CRT.[7,21,25] Of the total group of 175 patients, 122 women (69.7%) were diagnosed with squamous cell carcinoma, 46 (6.3%) with adenocarcinoma, three (1.7%) with adenosquamous carcinoma, and four (2.3%) with another histological subtype. Pelvic exenteration was performed in 19 patients (11%) and a hysterectomy was performed in 156 patients (89%). In total, 27%-100% of the patients had histologically confirmed residual disease in the salvage surgical specimen. Of the 131 patients operated with salvage surgery because of biopsy-confirmed residual disease, 72%-100% showed residual disease on the salvage surgery specimen. Of 44 patients who underwent surgery after only radiological assessment of the presence of residual disease without confirmatory biopsy, only 27%-48% showed residual disease on the salvage surgery specimen (Table 1).

A total of 105 complications were registered in 175 patients with salvage surgery. A total of 15 (9%) fistulas were reported, of which five were fistulas of the urinary tract, five were rectovaginal fistulas, two were vesicovaginal fistulas, and five were other fistulas. A total of 31 (18%) urinary tract complications were reported, for which six patients needed stenting or a surgical procedure, five patients had renal insufficiency, four had infections, two developed urinary incontinence, and 12 had other complications. A total of 17 (10%) gastrointestinal complications were reported, among which eight patients had radiation enteritis/proctitis, five of whom required surgery. A total of six (3%) infections were reported, four with sepsis. There were 36 (21%) other complications reported, two in patients who had undergone a re-laparotomy (Table 3).

The overall survival and recurrence rates were available for 159 patients. After salvage surgery, recurrence of disease was observed in 50 patients (31%) and four patients were alive with recurrent disease at the time that the studies were published. In total, 49 patients (31%) died. The recurrence and survival rates based on the 175 patients treated with salvage surgery were 29% and 28%, respectively. The mean follow-up period was 24.9 months based on the median follow-up period of four studies (Table 1).

Additional information on patients with recurrence of disease after salvage surgery was available for 14 of the 50 patients with recurrence.[7,21,25] No information was available for the other 36 patients with recurrence. Eleven patients were diagnosed with recurrent squamous cell carcinoma and three with recurrent adenocarcinoma. Eight patients died and four patients were alive with recurrent disease, two patients were successfully treated for recurrent disease and showed no evidence of disease at the time of publication of the article. The postoperative complications for patients with recurrence after salvage surgery are available for 10 patients, of whom seven had a complication (Table S2).

4 | DISCUSSION

This systematic review shows that a total of 27%-100% of patients with radiologically suspected or histologically confirmed residual disease had residual disease on the salvage surgery specimen. The women treated with salvage surgery based on residual disease on biopsy showed a higher percentage of positive pathology than the women treated with salvage surgery based on radiology findings alone. The risk of complications after salvage surgery is high. After salvage surgery, still 31% of the patients relapsed. The overall survival rate after salvage surgery is 69%, after a mean follow-up period of 24.9 months. Selection of patients who would benefit from salvage surgery and confirmation of residual disease with biopsy are pivotal before performing salvage surgery.

The validity of residual disease detection by MRI and PET-CT have been assessed by other studies and they are in agreement with our results. They confirmed that MRI is suboptimal in diagnosing residual disease with reported sensitivities ranging between 77.8% and 86.1%, and reported specificity between 35.5% and 55%.[26-28] Accuracy of residual disease detection by PET-CT scan was assessed by Ferrandina et al. They reported a sensitivity and specificity for PET-CT of 63.1% and 80.6%, respectively.[28] This concluded that neither MRI nor PET-CT was accurate in detecting residual disease in the cervix and selecting patients who might benefit from salvage surgery. Biopsy after CRT seems the most accurate procedure to detect residual disease, but timing of biopsies after radiation therapy is crucial. In our study, four studies performed salvage surgery after confirmation of residual disease on biopsy. Three studies confirmed the presence of residual disease in 100% of the salvage surgery

TABLE 1 Characteristics of included studies

Author (y), country of study	Inclusion period	Total number of patients with residual disease (patients with salvage surgery)	Reason for no salvage surgery	Age median/mean (range)	Stage	Histology
Azria (2005),[21] France	1999-2002	12 (10)	1 peritoneal carcinomatosis and 1 patient underwent surgical procedure outside the institution	Median 49 y (range 28-73 y)	IIA = 2 IIB = 8	SCC = 8 AC = 2
Platt (2013),[33] UK	2012-2016	15 (15)	–	Median 46.7 y (range 32-71 y)	IB2 = 2 IIA = 1 IIB = 9 IIIB = 3	SCC = 8 AC = 7
Boers (2014),[22] the Netherlands	1994-2011	84 (61)	13 inoperable tumors, 9 distant metastases 1 refused salvage surgery	Median 51 y (range 40-69 y)	IB = 4 IB2 = 16 IIA = 8 IIB = 29 IIIA = 2 IIIB = 2	SCC = 35 AC = 20 ASC = 2 Other = 4
Rema (2015),[23] India	2010-2014	23 (20)	3 inoperable: 2 para-aortic nodal metastases 1 pelvic side wall involvement	Median 43 y (range 28-63 y)	IB = 7 IIA = 4 IIB = 8 IIIA = 1	SCC = 17 AC = 3
Gosset (2019),[25] France	2004-2013	31 (29)	2 histological subtypes (small-cell carcinoma and neuroendocrine tumor	Median 45.8 y (range 30-63 y)	IB2 = 8 IIA = 2 IIB = 18 III = 1	SCC = 22 AC = 7
Pervin (2019),[7] Bangladesh	2009-2013	55 (40)	15 distant disease	Mean 45.1 y	IIB = 25 IIIB = 7 At least IIB = 8	SCC = 32 AC = 7 ASC = 1
Total		220 (175)	2 histological subtypes 13 inoperable 28 distant metastases 1 surgery in other hospital 1 refused salvage surgery		IB = 11 IB2 = 26 IIA = 17 IIB = 97 III = 1 IIIA = 3 IIIB = 12 At least IIB = 8	SCC = 122 AC = 46 ASC = 3 Other = 4

Abbreviations: AC, adenocarcinoma; ASC, adenosquamous carcinoma; BT, brachytherapy; CC, cervical cancer; CRT, chemoradiation therapy; EBRT, external-beam radiation therapy; ICRT, intracavitary radiation therapy; IQR, interquartile range; SCC, squamous cell carcinoma.

[a]Two patients received a lateral pelvic radiation boost of 8 and 10 Gy, because of bulky nodes.

[b]One patient received four cycles of chemotherapy. Five patients did not receive the planned dose BT: four patients did not receive the last treatment and one patient declined all BT treatments.

[c]Nine patients were only treated with radiation therapy.

[d]Fourteen patients received three cycles of neoadjuvant cisplatin and EBRT. Nine patients received three cycles of neoadjuvant cisplatin, EBRT and BT. Six patients received concurrent cisplatin and EBRT. Three patients received concurrent cisplatin, EBRT and BT. Eight patients received EBRT.

[e]The survival and recurrence rate are only reported for the patients with residual disease.

[f]Survival and recurrence rates were calculated based on 159 patients with known survival rates.

CRT	Diagnostic procedure residual disease	Time until salvage surgery	Salvage surgery	Positive pathology after salvage surgery (%)	Follow-up period median/mean (range)	Recurrence	Death
EBRT 45 Gy with concomitant cisplatin 40 mg/m^2) with 15 Gy BT[a]	Histologically confirmed	Median 49 d (range 42-64 d) after BT	1 exenteration 9 hysterectomy	10 (100%)	Median 22 mo (range 1-37 mo) 1 patient lost to follow up	7	4 1 patient lost to follow up
EBRT 51 Gy in 28 fractions with concomitant at least 5 cycles cisplatin (40 mg/m^2) with 3 doses BT[b]	MRI and in some cases biopsy	MRI 8 wk after CRT and salvage surgery "few" weeks after CRT	15 hysterectomy	4 (26.7%)	Median 31 mo (range 12-60 mo)	3	1
EBRT 45 Gy in fractions of 1.8 Gy, from 1994 additional BT total dose 34.8 Gy. Before 1999 carboplatin (300 mg/m^2) and 5 FU (600 mg/m^2). After 1999 cisplatin 40 mg/m^2)[c]	Biopsy with CT-scan and PET-CT	Unknown	5 pelvic exenteration 56 hysterectomy	44 (72%)	Median 27.6 mo (IQR, 15.6-56.4 mo)	31 25 local and 6 distant	29 27 CC and 2 of unknown cause
EBRT 40-46 Gy in 20-23 fractions and concomitant cisplatin (40 mg/m^2) with 3 × 7 Gy BT	Biopsy with MRI and PET-CT in 8 cases	Unknown	13 pelvic exenteration 7 hysterectomy	20 (100%)	Median 19 mo (range 9-53 mo)	2	11
EBRT 45-50.4 Gy in 25-28 fractions of 1.8 Gy over 5 wk with concomitant cisplatin (40 mg/m^2) with 15 Gy BT	Clinical evaluation with pelvic MRI and/or PET-CT. Some patient's cytology and biopsy	Median of 76 d (range, 56-84 d) after BT	29 hysterectomy	14 (48.3%)	Unknown	3 distant[e]	3[e]
EBRT 50 Gy in 25 fractions of 2 Gy for 25 d with or without 3 × 7 Gy BT. 23 patients received three doses cisplatin[d]	Biopsy with MRI or CT	14-18 wk after CRT	40 hysterectomy	40 (100%)	Mean 93.6 mo	4; 3 local and 1 distant	1
			19 pelvic exenteration 156 hysterectomy	132	Mean 24.9 mo based on median of 4 studies	50 (31%)[f]	49 (31%)[f]

TABLE 2 Newcastle-Ottawa Scale for cohort studies

	Selection				Comparability	Outcome			
Article	Representativeness of the exposed cohort[a]	Selection cohorts same source	Ascertainment of exposure[b]	Outcome of interest was not present at start of study	Comparability of cohorts	Assessment of outcome[c]	Follow up[d]	Adequacy of follow up	Quality
Azria (2005)[21]	★	NA	★	★	NA	★	★ 22 mo (range 1-37 mo)	★ 1 patient lost to follow up	Good
Platt (2013)[33]	★	NA	★	★	NA	★	★ 31 mo (range 12-60 mo)	★ No lost to follow up	Good
Boers (2014)[22]	★	★ Drawn from the same community as the exposed cohort	★	★	★	★	★ 27.6 mo (IQR, 15.6-56.4 mo)	★ No lost to follow up	Good
Rema (2015)[23]	★	NA	★	★	NA	★	★ 19 mo (range 9-53 mo)	No statement about lost to follow up	Fair
Gosset (2019)[25]	★	NA	★	★	NA	★	No statement about follow up period	No statement about lost to follow up	Fair
Pervin (2019)[7]	★	NA	★	★	NA	★	★ 93.6 mo (mean)	No statement about lost to follow up	Fair

Abbreviation: NA, not applicable.

[a]Representativeness of the exposed cohort: all included studies representative for women with residual cervical cancer after chemoradiation therapy treated with salvage surgery.

[b]Ascertainment of exposure: all with database or medical records.

[c]Assessment of outcome: all with medical records.

[d]Follow-up period ≥12 mo was assessed as long enough for outcomes to occur.

TABLE 3 Complications after salvage surgery

Author (y)	Total number of patients with salvage surgery	Fistula	Urinary tract	Gastrointestinal	Infection	Other	Total
Azria (2005)[21]	10	2 ureteral; 1 rectovaginal	4 ureteral stenosis requiring stenting or surgical procedure; 1 bladder retention; 1 incontinence of the bladder			1 pulmonary embolism; 2 lymphocyst; 1 iliac phlebitis;	13
Platt (2013)[33]	15	1 enterovesical; 1 vesicovaginal	1 urinary incontinence; 2 radiation cystitis; 2 ureteric fibrosis with 1 with stents and 1 with nephrostomy	3 chronic diarrheas; 1 rectal bleeding; 2 radiation proctitis		3 chronic pelvic back pain; 2 anxiety and depression; 1 ongoing fatigue	19
Boers (2014)[22]	61	3 fistulas (rectovaginal, vesicovaginal)	6 urological problems (disabling incontinence hematuria requiring blood transfusion, ureteral stenosis)	1 rectal bleeding; 4 gastrointestinal (impairing diarrhea and obstipation problems, radiation enteritis, ileus); 5 radiation enteritis requiring surgery	4 sepsis	2 neurological pain; 1 frozen pelvis; 2 relaparotomy; 16 mild grade 1 complications	44
Rema (2015)[23]	20	2 urinary; 1 uterovaginal fistula	3; pyelonephritis; 5 renal insufficiency; 1 repeated urinary tract infection; 1 bladder atony				13
Gosset (2019)[25]	29	1 rectovaginal and bladder; 2 rectovaginal; 1 ureteral			1 pelvic abscess; 1 chylous ascites	1 lymphocele with renal obstruction	7
Pervin (2019)[7]	40		1 urinary retention; 2 urinary stenosis; 1 bladder injury	1 rectal injury		3 lymphedemas; 1 vascular injury	9
Total	175	15 fistulas (9%)	31 urinary tract problems (18%)	17 gastrointestinal problems (10%)	6 (3%)	36 (21%)	105

pathology specimens.[7,21,23] The study by Boers et al confirmed the presence of residual disease in salvage surgery specimens in 72% of women.[22] In this study, biopsies were taken 8-10 weeks after CRT and the time until salvage surgery was not described. When biopsies are taken too early, cervical cancer is still going into regression due the continuing effect of the radiation therapy. This could lead to a higher percentage of false-positive residual disease. Hoeijmakers et al stated that post-CRT biopsies should be taken 12-16 weeks after completion of CRT, in medically fit patients without signs of metastases. Histological confirmation of residual disease a sufficient time after CRT reduces unnecessary salvage surgery and hence unnecessary complications.[29]

Studies reported that most of the complications after salvage surgery were due to the unpredictable healing capacity of previously irradiated tissue.[30] But sometimes it is unclear if complications are related to the CRT or to the salvage surgery. After salvage pelvic exenteration, even higher complication rates are reported in comparison with salvage hysterectomy.[23] Most of the complications occurring after salvage surgery can influence the quality of life of patients. One of the major complications that can influence the quality of life of patients is fistula, with symptoms such as hygiene problems, pain, recurrent vaginal or urinary tract infections, and pain during sexual intercourse. Forsgren and Altman reported that fistulas occurred in 1%-4% of patients treated with radical hysterectomy without CRT therapy.[31] In our study, a total of 9% of patients had fistulas, which is higher than the reported number after radical hysterectomy. This is probably because the salvage surgery took place in an irradiated area and some patients were treated with salvage exenteration instead of salvage hysterectomy. Fistulas of the female urogenital tract can be a challenging condition to treat and often require repeat surgery.[31] Because of the high impact on the quality of life of patients after salvage surgery, and the low sensitivity and specificity of radiological scans to confirm residual disease, we advise patients and physicians to histologically prove residual disease after CRT before treating patients with salvage surgery.

Two previously published articles showed that adjuvant hysterectomy after CRT therapy does not improve overall survival, although it seemed to reduce the risk of recurrence.[13,14] According to Shim et al, the 5-year overall survival after CRT is approximately 70%.[14,32] In this systematic review, the overall survival after salvage surgery was 69% after a mean follow-up period of 24.9 months based on the median of four studies. Patients with residual disease after primary treatment are generally a non-favorable group of patients. The prognosis of patients with residual disease and without residual disease cannot be compared based on survival outcomes. Before salvage surgery is performed, patients should be clearly informed of the potential complications of salvage surgery and the fact that we have little knowledge on the impact of salvage surgery on survival outcomes.

The strengths of this study are the comprehensive search strategy and the study design, ensuring that the assessment of the articles and the data extraction were performed independently by two reviewers. The quality assessment of this review shows a good or fair quality of the included articles, indicating a low methodological bias risk. This review provides relevant information about salvage surgery after CRT therapy and provides information about the complication risks of salvage surgery. This ensures that a well-considered treatment choice can be made by patients and clinicians. The evaluation of data is not without limitations, there is some heterogenicity between the included studies. First, there is a wide inclusion period (1994-2016) of the included studies. Therefore, some of the patients included were diagnosed with LACC according an earlier FIGO staging system. For that reason, 30.9% of the patients included in our study are diagnosed with stage IB-IIA and received CRT with salvage surgery. During these years, CRT and salvage surgery have undergone significant changes, and diagnostic techniques have improved, which can result in other survival outcomes. Second, one study included five patients with incomplete primary therapy but without diagnostic residual disease and treated these patients with salvage surgery.[33] Third, not all patients received a biopsy within the same timeframe after CRT. Patients who receive a biopsy at an earlier time after CRT therapy have a higher chance of false-positive biopsy results and may undergo unnecessary salvage surgery. Fourth, not all studies performed the same type of salvage surgery; this could influence the completeness of the surgery and risk of complications. Fifth, not all studies reported all the complications systematically. There are a limited number of grade 1 complications registered in the studies. Some studies only reported complications with Grade 3a or more according to the Dindo classification system.[25] This implicates an underestimation of the risk of complications reported in this review. We expect Grade 1 complications to be more prevalent as ongoing fatigue and depressed feelings are quite common in women who underwent salvage surgery. Additionally, not all reported complications in this systematic review are due to the salvage surgery, some complications like radiation enteritis/proctitis are due to the radiation therapy.[7] Sixth, some studies stated the survival rate for all the patients with salvage surgery and not only those with histologically confirmed residual disease in the final pathology specimen.[7,22]

5 | CONCLUSION

Our systematic review provides information for women and clinicians on the potential impact of salvage surgery after CRT. Cervical biopsy after CRT seems the most accurate procedure to detect residual disease and operating without histological confirmation of residual disease should be avoided. If surgery can be prevented, complications related to surgery can be prevented. A thorough selection of patients and extensive counseling on survival benefits and complications risk are recommended.

CONFLICT OF INTEREST

The authors have stated explicitly that there is no conflict of interest in connection with this article.

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REFERENCES

1. WHO. Cervical cancer [Internet]. 2019. https://www.WHO.int/cancer/prevention/diagnosis-screening/cervical-cancer/en/. Accessed December 2, 2019
2. UNAIDS [Internet]. 2019. https://www.unaids.org/en/resources/presscentre/featurestories/2019/february/20190204_cervical-cancer. Accessed December 3, 2019
3. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *Int J Gynecol Obstet*. 2018;143:22-36.
4. Cancer Research UK. Cancer Statistics for the UK [Internet]. https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk. Accessed January 14, 2020
5. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*. 1999;340:1144-1153.
6. Green JA, Kirwan JM, Tierney JF, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet*. 2001;358:781-786.
7. Pervin S, Ruma FI, Rahman K, et al. Adjuvant hysterectomy in patients with residual disease after radiation for locally advanced cervical cancer: a prospective longitudinal study. *J Glob Oncol*. 2019;5:1-7.
8. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med*. 1999;340:1154-1161.
9. Alberts DS, Brady M, Cikaric S, et al. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: Individual patient data meta-analysis. *Cochrane Database Syst Rev*. 2010;20:CD008285.
10. Quinn MA, Benedet JL, Odicino F, et al. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynecol Obstet*. 2006;95(Supp 1):43-103.
11. Lèguevaque P, Motton S, Delannes M, et al. Completion surgery or not after concurrent chemoradiotherapy for locally advanced cervical cancer? *Eur J Obstet Gynecol Reprod Biol*. 2011;155:188-192.
12. Fanfani F, Vizza E, Landoni F, et al. Radical hysterectomy after chemoradiation in FIGO stage III cervical cancer patients versus chemoradiation and brachytherapy: complications and 3-years survival. *Eur J Surg Oncol*. 2016;42:1519-1525.
13. Shi D, Liang Z, Zhang C, Zhang H, Liu X. The effect of surgery on the survival status of patients with locally advanced cervical cancer after radiotherapy/chemoradiotherapy: a meta-analysis. *BMC Cancer*. 2018;8:308.
14. Shim S-H, Kim S-N, Chae SH, Kim JE, Lee SJ. Impact of adjuvant hysterectomy on prognosis in patients with locally advanced cervical cancer treated with concurrent chemoradiotherapy: a meta-analysis. *J Gynecol Oncol*. 2018;29:e25.
15. Viswanathan AN, Lee LJ, Eswara JR, et al. Complications of pelvic radiation in patients treated for gynecologic malignancies. *Cancer*. 2014;120:3870-3883.
16. Ota T, Takeshima N, Tabata T, Hasumi K, Takizawa K. Adjuvant hysterectomy for treatment of residual disease in patients with cervical cancer treated with radiation therapy. *Br J Cancer*. 2008;99:1216-1220.
17. Coleman RL, Keeney ED, Freedman RS, Burke TW, Eifel PJ, Rutledge FN. Radical hysterectomy for recurrent carcinoma of the uterine cervix after radiotherapy. *Gynecol Oncol*. 1994;55:29-35.
18. Xiao M, Gao H, Bai H, Zhang Z. Quality of life and sexuality in disease-free survivors of cervical cancer after radical hysterectomy alone. *Medicine*. 2016;95:e4787.
19. Ashing-Giwa KT, Lim J-W, Tang J. Surviving cervical cancer: does health-related quality of life influence survival? *Gynecol Oncol*. 2010;118:35-42.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine*. 2009;2009(6):e1000097.
21. Platt SL, Patel A, Humphrey PJ, Al-Booz H, Bailey J. Completion surgery after chemoradiotherapy for cervical cancer–is there a role? UK Cancer Centre experience of hysterectomy post chemo-radiotherapy treatment for cervical cancer. *J Obstet Gynaecol*. 2019;39:68-73.
22. Gosset M, Chargari C, Bentivegna E, et al. Should we cease to perform salvage hysterectomy after chemoradiation and brachytherapy in locally advanced cervical cancer? *Anticancer Res*. 2019;39:2919-2926.
23. Azria E, Morice P, Haie-Meder C, et al. Results of hysterectomy in patients with bulky residual disease at the end of chemoradiotherapy for stage IB2/II cervical carcinoma. *Ann Surg Oncol*. 2005;12:332-337.
24. Boers A, Arts HJG, Klip H, et al. Radical surgery in patients with residual disease after (chemo)radiation for cervical cancer. *Int J Gynecol Cancer*. 2014;24:1276-1285.
25. Rema P, Mathew AP, Suchetha S, Ahmed I. Salvage surgery for cervical cancer recurrences. *Indian J Surg Oncol*. 2017;8:146-149.
26. Wells GA, Shea B, O'Connell D, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Ontario: University of Ottawa; 2019.
27. Hequet D, Marchand E, Place V, et al. Evaluation and impact of residual disease in locally advanced cervical cancer after concurrent chemoradiation therapy: results of a multicenter study. *Eur J Surg Oncol*. 2013;39:1428-1434.
28. Ferrandina G, Ercoli A, Fagotti A, et al. Completion surgery after concomitant chemoradiation in locally advanced cervical cancer: a comprehensive analysis of pattern of postoperative complications. *Ann Surg Oncol*. 2014;21:1692-1699.
29. Ferrandina G, Petrillo M, Restaino G, et al. Can radicality of surgery be safely modulated on the basis of MRI and PET/CT imaging in locally advanced cervical cancer patients administered preoperative treatment? *Cancer*. 2012;118:392-403.
30. Hoeijmakers YM, Zusterzeel PLM, Snyers A, Ham MAPCv, Bekkers RLM. Cervical biopsy after chemoradiation for locally advanced cervical cancer to identify residual disease: a retrospective cohort study. *J Surg Oncol*. 2019;2:2-6.
31. Höckel M, Dornhöfer N. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. *Lancet Oncol*. 2006;7:837-847.
32. Forsgren C, Altman D. Risk of pelvic organ fistula in patients undergoing hysterectomy. *Curr Opin Obstet Gynecol*. 2010;22:404-407.
33. Shim S-H. Adjuvant hysterectomy in patients with locally advanced cervical cancer treated with concurrent chemoradiotherapy. *J Gynecol Oncol*. 2019;30:35-42.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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