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Primary surgery versus primary radiotherapy with or without chemotherapy for early adenocarcinoma of the uterine cervix (Review)

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[Intervention Review]

Primary surgery versus primary radiotherapy with or without chemotherapy for early adenocarcinoma of the uterine cervix

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ABSTRACT

Background

For early squamous cell carcinoma of the uterine cervix, the outcome is similar after either primary surgery or primary radiotherapy. There are reports that this is not the case for early adenocarcinoma (AC) of the uterine cervix: some studies have reported that the outcome is better after primary surgery. There are no systematic reviews about surgery versus chemoradiation in the treatment of cervical cancer.

Objectives

The objectives of this review were to compare the effectiveness and safety of primary surgery for early stage AC of the uterine cervix with primary radiotherapy or chemoradiation.

Search methods

We searched Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3, 2009, MEDLINE (1950 to July week 5, 2009), EMBASE (1980 to week 32, 2009) and we also searched the related articles feature of PubMed and the Web of Science. We also checked the reference lists of articles. For this update, the searches were re-run in June 2012: CENTRAL Issue 6, 2012, Cochrane Gynaecological Specialised Register June 2012, MEDLINE 2009 to June week 2, 2012 and Embase 2009 to 2012 week 24. Most recent searches were re-run in November 2020: CENTRAL Issue 11, 2020, MEDLINE up to November week 2, 2020 and Embase up to 2020 week 47.

Selection criteria

Studies of treatment of patients with early AC of the uterine cervix were included. Treatment included surgery, surgery followed by radiotherapy, radiotherapy and chemoradiation.

Data collection and analysis

Forty-three studies were selected by the search strategy and 30 studies were excluded. Twelve studies were considered for inclusion. Except for one randomised controlled trial (RCT), all other studies were retrospective cohort studies with variable methodological quality and had limitations of a retrospective study. Comparing the results from these retrospective studies was not possible due to diverging treatment strategies. Only follow-up data for the one included study was identified in the Novemeber 2020 search.

Main results

Analysis of a subgroup of one RCT showed that surgery for early cervical AC was better than radiotherapy. However, the majority of operated patients required adjuvant radiotherapy, which is associated with greater morbidity. Furthermore, the radiotherapy in this study was not optimal, and surgery was not compared to chemoradiation, which is currently recommended in most centres. Finally, modern imaging

techniques (i.e. magnetic resonance imaging (MRI) and positive emission tomography - computed tomography (PET-CT) scanning) allow better selection of patients and node-negative patients can now be more easily identified for surgery, thereby reducing the risk of 'double trouble' caused by surgery and adjuvant radiotherapy.

Authors' conclusions

We recommend surgery for early-stage AC of the uterine cervix in carefully staged patients. Primary chemoradiation remains a second best alternative for patients unfit for surgery; chemoradiation is probably first choice in patients with (MRI or PET-CT-suspected) positive lymph nodes. Since the last version of this review no new studies were found. Twenty-year follow up data in 2017 confirmed these results.

PLAIN LANGUAGE SUMMARY

Surgery or radiotherapy for early cervical cancer of the adenocarcinoma type

Early-stage cervical cancer of the common type, squamous cell carcinoma, has the same prognosis after primary surgery or radiotherapy. For cervical cancer of the glandular cell type (adenocarcinoma) we recommend surgery. Second best alternative for patients unfit for surgery is chemoradiation. For patients with suspected positive lymph nodes, chemoradiation is probably the first choice.

BACKGROUND

Description of the condition

This is an updated version of the original Cochrane review published in Cochrane Database of Systematic Reviews. 2013 Jan 31;2013(1):CD006248. doi: 10.1002/14651858.CD006248.pub3.

Cervical cancer is the second most common cancer among women worldwide (Ferlay 2004). The prognosis of patients with cervical cancer depends on FIGO (International Federation of Gynecologists and Obstetricians) (Benedet 2001) stage at time of diagnosis, presence of lymph node metastases, tumour size and histological type (Baalbergen 2004; Chen 1998; Kasamatsu 2009). The three major histological types of invasive cervical cancer are squamous cell carcinomas (SCC), adenocarcinomas (AC) and adenosquamous carcinoma (ASC). SCC comprises 80% of cases, and AC and ASC comprise approximately 15% (ACOG 2002). Over the past 40 years the relative proportion and absolute incidence of AC compared to SCC has increased, especially in women younger than 35 years (Alfsen 2000; Chan 2003; Krane 2001; Liu 2001; Schoolland 2002; Vizcaino 1998).

Screening for SCC has effectively reduced both incidence and mortality of invasive squamous cancer by early detection and treatment of pre-invasive lesions (Smith 2000). Although screening reduces mortality from cervical AC, the incidence remains unaltered (Nieminen 1995). It remains controversial whether or not patients with AC have a worse prognosis. The literature is inconsistent; some studies report a similar prognosis for AC of the uterine cervix and SCC (Grisaru 2001; Ishikawa 1999; Kilgore 1988) whereas others report a poorer prognosis for AC (Bulk 2003; Eifel 1995; Hopkins 1991). Questions remain about what factors account for this apparent poorer prognosis. Cervical AC may metastasise earlier (Lea 2002) or may be detected later (Drescher 1989; Hurt 1977). It may respond less well to radiotherapy (Hong 2000; Hurt 1977), have a higher incidence of relapse and the treatment of recurrent disease less successful (Kasamatsu 2002; Lai 1999) or possibly the inclusion of special subtypes such as clear cell carcinoma could account for this difference in prognosis (Look 1996).

Description of the intervention

Treatment protocols used for SCC and AC are similar and therapy is based on clinical staging according to FIGO (Benedet 2001). Due to recent developments in imaging such as magnetic resonance imaging (MRI) and developments of surgical techniques such as endoscopy, the current FIGO classification for cervical cancer has been revised (Pecorelli 2009). Micro-invasive disease is managed by cone biopsy or hysterectomy. Radical hysterectomy (removal of the uterus with adjacent tissue and draining pelvic lymph nodes) has become standard management for the majority of early cervical cancers, but external beam irradiation along with a vaginal application of brachytherapy to the cervix has been increasingly employed for bulky stage I and II disease (tumour diameter of more than four centimetres). Both external beam irradiation and brachytherapy have undergone rapid developments, of which the therapeutic consequences are not yet clear. Intensity-modulated radiotherapy (IMRT) allows more conformal external beam dose delivery to the clinical target (uterine cervix and regional pelvic lymph nodes) thereby sparing critical organs (bladder and intestines). IMRT requires an accurate definition and delineation of clinical target (Small 2008; Taylor 2005; Taylor 2007; Vizcaino 1998). Paradoxically, in clinical practice, compared to 'old fashioned' four-field box-technique defined by osseous anatomical structures (Fletcher 1973), image-guided target definition has increased rather than decreased the irradiated volumes for radiotherapy of pelvic tumours. The historical low dose rate (LDR) brachytherapy techniques using radium and caesium have largely been replaced by iridium as the radioactive source. Iridium allows high dose rate (HDR) and pulsed dose rate (PDR), which both have decreased irradiation time and patient burden. These techniques, particularly if combined with intraoperative MRI, have reduced the risk of misplacement of the brachytherapy applicator, and allow image-guided brachytherapy, thereby increasing local control whilst reducing toxicity (Georg 2009).

After primary surgery, it may be useful to add radiotherapy (in up to 50% of operated patients depending on the selection criteria of the series). In primary radiotherapy in selected cases, adjuvant surgery (salvage hysterectomy) may be performed if the tumour recurs locally (Weiner 1975). The use of both surgery and radiotherapy leads to more severe morbidity (Barter 1989; Landoni 1997) than either used alone. Complications of radical hysterectomy are chronic bladder dysfunction (3% to 13%), ureterovaginal or vesicovaginal fistula (1% to 2%), pulmonary embolism (1% to 2%), small bowel obstruction (1%), lymphocoele formation (5% to 8%) and hydroureter nephrosis (3%). Complications of radiotherapy arise later but are often permanent: proctitis (7.6%), radiation colitis, early menopause, sexual dysfunction, shortening and fibrosis of the vagina, oedema of the legs (0.6%), hydroureter nephrosis (5%) and vesicovaginal fistula (1.4%). The combination of radical surgery followed by radiotherapy carries the worst morbidity: hydroureter nephrosis (10%), severe oedema of the legs (9%), lymphocoele formation (15%), ureterovaginal or vesicovaginal fistula (7.4%) and vesical complications and bowel morbidity (Boronow 1971; Kucera 1998 Landoni 1997; Waggoner 2003).

Why it is important to do this review

In 1999, after the publication of four randomised controlled trials (RCTs) on this issue (Keys 1999; Morris 1999; Rose 1999; Whitney 1999) the US National Cancer Institute (NCI) issued an alert indicating that combined chemoradiation should be considered for all patients with cervical cancer who previously would be treated with radiotherapy. In 2001, a Cochrane review showed concomitant chemotherapy and radiotherapy improved overall survival (OS) and progression-free survival (PFS) in locally advanced cancer (Green 2001; Green 2005).

For early SCC, the outcome is similar after either primary surgery or primary radiotherapy (Hopkins 1991; Landoni 1997). There are reports that this is not the case for early AC of the uterine cervix and some studies have reported that the outcome is better after primary surgery (Chen 1999; Kucera 1998). Currently there are no systematic reviews comparing surgery versus chemoradiation in the treatment of cervical cancer.

OBJECTIVES

To compare the effectiveness and safety of primary surgery for early-stage AC of the uterine cervix with primary radiotherapy or chemoradiation.

METHODS

Criteria for considering studies for this review

Types of studies

It was anticipated that only a very small number of RCTs, the preferred type of study, would have been conducted on cervical cancer treatment. Therefore, observational studies, non-randomised studies with concurrent controls and studies with historical controls were also considered for incorporation in this review. The methodological quality of non-RCTs was assessed on the basis of comparability of treatment groups at baseline, adjustment for potential confounders and allocation of the treatment.

Types of participants

Patients with histological confirmed early-stage AC of the uterine cervix were included. For the purpose of this review early-stage AC was defined as cancer in which the primary tumour was confined to the cervix and upper two-thirds of the vagina or the parametrium (FIGO stage IA to IIB). For FIGO staging see Appendix 1.

Types of interventions

The following surgical interventions were studied:

- extrafascial hysterectomy or Rutledge class I hysterectomy, which is defined as removal of all cervical tissue by incision of the pubocervical ligament allowing reflection and retraction of the ureters laterally without actual dissection from the ureteral bed;
- Rutledge class II extended hysterectomy, which is defined as the removal of the medial half of the cardinal and uterosacral ligaments and upper third of the vagina. It is usually combined with a pelvic lymphadenectomy;
- radical hysterectomy or Rutledge class III extended hysterectomy, which can be defined as the removal of the entire cardinal and uterosacral ligaments and removal of the upper third of the vagina and a pelvic lymphadenectomy (Piver 1974).

The following radiotherapy interventions were studied:

- whole pelvis radiotherapy, defined as external beam radiation in which the clinical target volume (CTV) encompasses the cervix, the uterus, the upper two-thirds of the vagina, the parametria and the draining lymph nodes at risk, up to the level of lumbar spine 5 and sacral spine 1;
- vaginal application of a radioactive source to the cervix (brachytherapy). There are different brachytherapy techniques that apply the radioactive source for short periods of time or for several days;
- chemoradiation, which is defined as concomitant radiotherapy and cytotoxic chemotherapy.

Any comparison of a surgical intervention with a radiotherapy intervention was considered.

Types of outcome measures

Primary outcomes

The primary outcomes were OS and disease-free survival (DFS).

Secondary outcomes

Secondary outcomes of interest were adverse effects of treatment as intestinal, urogenital and premature menopausal complications and quality of life (QoL).

Search methods for identification of studies

Electronic searches

The literature search was carried out according to the criteria set by the Cochrane Gynaecological Cancer Review Group. There were no language restrictions. Searches of Cochrane Central Register of Controlled Trials (CENTRAL Issue 3, 2009), MEDLINE (1950 to July week 5 2009) and EMBASE (1980 to week 32 2009). Searches of the Group's Specialised Register and Non-Trials Database was devised using the groups coding system, was carried out on 6 July 2009.

Subsequent searches were run in June 2012 (CENTRAL Issue 6, 2012, Specialised Register June 2012, MEDLINE 2009 to June week 2, 2012 and Embase 2009 to 2012 week 24). Most recent searches were re-run in November 2020: CENTRAL Issue 11, 2020, MEDLINE up to November week 2, 2020 and Embase up to 2020 week 47.

For the search strategy we used a combination of free text and indexed terms and included an extended RCT filter to include cohort and case control studies (which also picked up follow-up, retrospective and prospective studies). See Appendix 2; Appendix 3; Appendix 4; Appendix 5.

The Web of Science and the register of ongoing controlled trials were checked (www.controlled-trials.com). The reference lists of the selected publications were searched. All relevant articles found were identified on PubMed, and using the 'related articles' feature, a further search was carried out for newly published articles.

Searching other resources

A handsearch of publications on the treatment of cervical cancer in the following journals was carried out: CME Journal of Gynecologic Oncology (from 1995), International Journal of Gynecologic Cancer (from 1993). Abstracts from conferences on gynaecological cancer (IGCS, SGO) and the British Library's Inside Conferences were checked.

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching were downloaded to a reference management database (Reference Manager 11), duplicates were removed and the remaining references were examined by two review authors (AB, YV) independently. Those studies that clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. The eligibility of retrieved papers was assessed independently by two review authors (AB, YV). Reasons for exclusion were documented. The number of references excluded is reported in a QUOROM flow chart (Figure 1 and Figure 2).

Figure 1. Quorum statement flow diagram

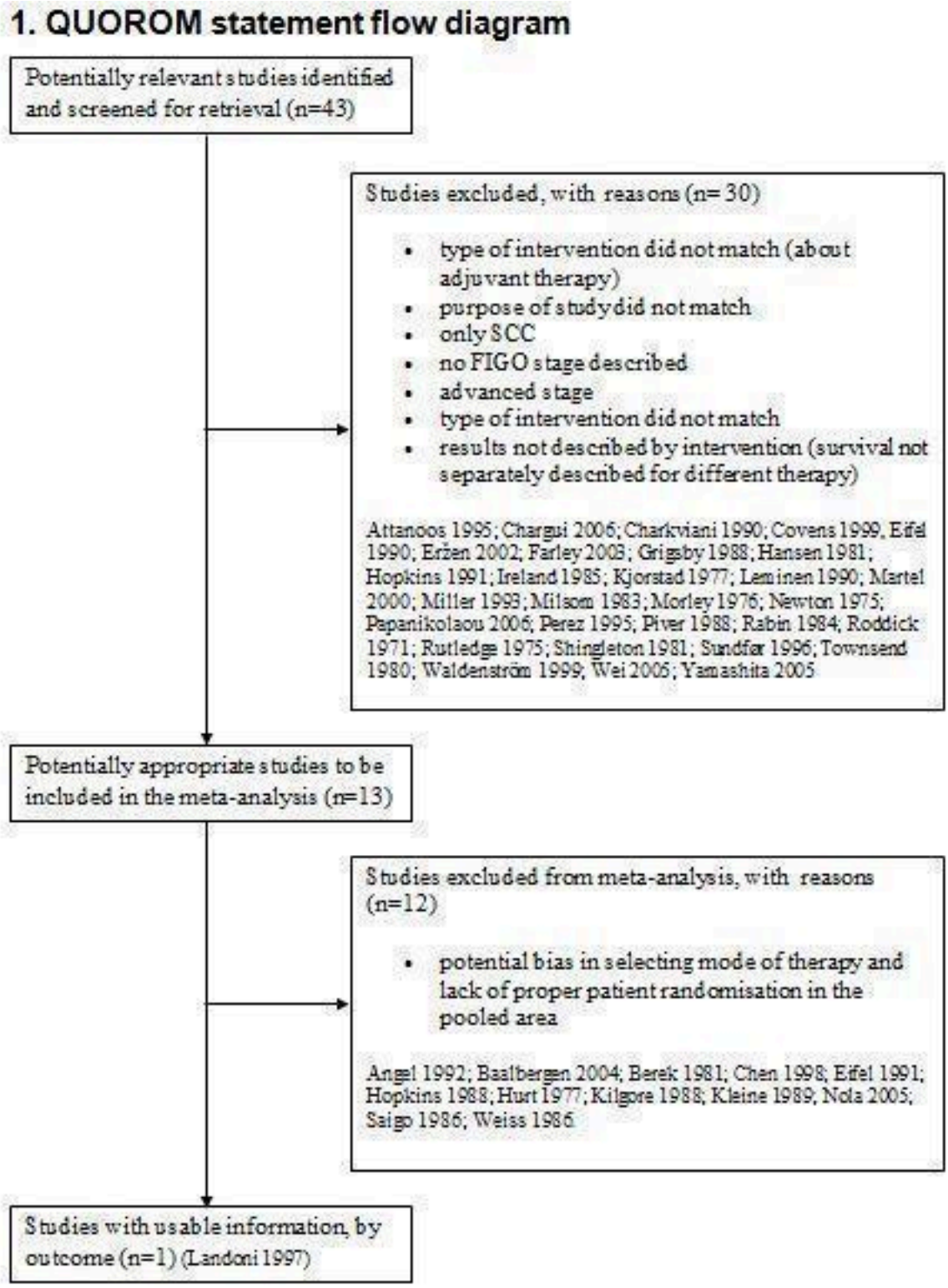
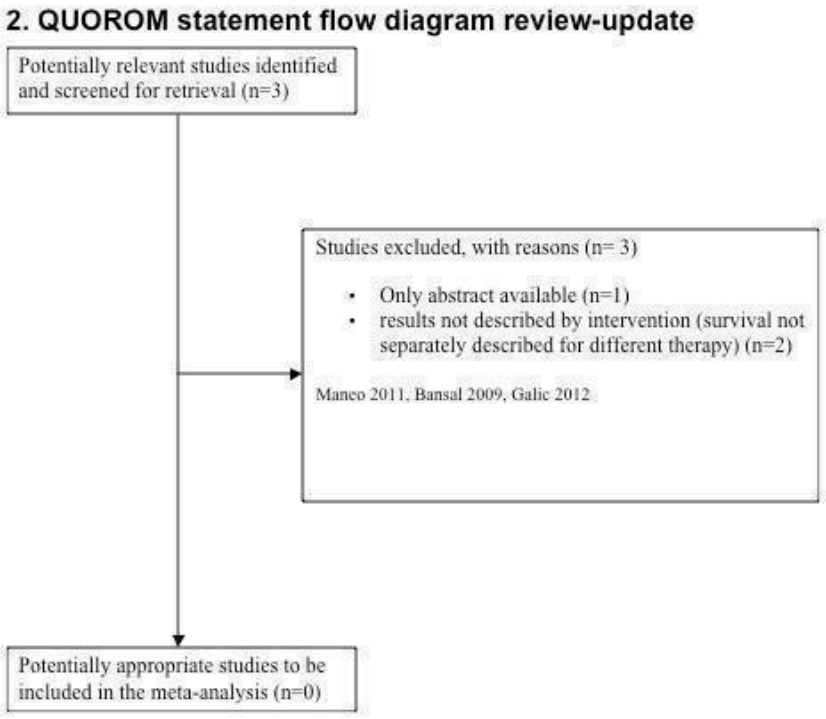


Figure 2. QUOROM statement flow diagram for update



Data extraction and management

For included studies, data on characteristics of patients and interventions (surgery, radiotherapy, chemotherapy), study quality and end points were abstracted independently by two review authors (AB and YV) onto data abstraction forms (Table 1; Table 2; Table 3; Table 4) that were developed for the review. Differences between review authors were resolved by discussion or by appeal to a third review author (AA) if necessary. No effort was made to blind the review authors of names of investigators, institutions, journals, etc. The data abstraction forms were designed a priori and were filled out independently.

Participants

For each trial, data on the number of patients assigned to each treatment, analysed and excluded from the investigators' analyses was extracted independently. The distribution of patients by age, stage, histology, grade and performance status was abstracted where available.

Interventions

Data on the type of surgery was be collected. Details of dose and fractionation of external beam radiotherapy and details of the brachytherapy dose, insertions and dose rate were collected. Details of any chemotherapy given concomitantly with radiotherapy were recorded. Details on duration or follow-up and ascertainment of long-term toxicity were also recorded.

Outcomes

For time to event (OS and recurrence-free survival) data, we extracted the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these were not reported, we attempted to estimate them from other reported statistics using the methods of Parmar 1998. For dichotomous outcomes (e.g. adverse events or deaths) if it was not possible to use an HR, we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at end point, in order to estimate a risk ratio (RR). For continuous outcomes (e.g. QoL), we extracted the final value and standard deviation (SD) of the outcome of interest and the number of patients assessed at end point in each treatment arm at the end of follow-up, in order to estimate the mean difference (MD) (if trials measured outcomes on the same scale) or standardised mean differences (SMD) (if trials measured outcomes on different scales) between treatment arms and its standard error. If reported, both unadjusted and adjusted statistics were extracted. Where possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis, in which participants were analysed in groups to which they were assigned. The time points at which outcomes were collected and reported were noted.

Assessment of risk of bias in included studies

An assessment of the risk of bias of included RCTs was assessed using the following criteria.

Blinding

We coded separately the blinding of patients, treatment providers and outcome assessors as:

- yes;
- no;
- unclear.

Randomisation

We coded the randomisation of participants to intervention groups as:

- adequate, for example a computer-generated random sequence or a table of random numbers;
- inadequate, for example date of birth, clinic identification number or surname;
- unclear, for example not reported.

Allocation concealment

We coded the concealment of allocation sequence from treatment providers and participants as:

- adequate, for example where the allocation sequence could not be foretold (A);
- unclear, for example not reported (B);
- inadequate, for example the computer-generated random sequence was displayed so treatment providers could see which arm of the trial the next participant was assigned to, or kept in a sealed opaque envelope (C).

Loss to follow-up

We recorded the number of participants in each intervention arm whose outcomes were not reported at the end of the study; we noted if loss to follow-up was not reported.

Risk of bias were assessed as above with the exception of randomisation and additionally assessed on the basis of:

- Comparability of treatment groups at baseline:
  - yes;
  - no;
  - unclear.
- Adjustment for potential confounders:
  - yes;
  - no;
  - unclear.

Assessment of heterogeneity

Heterogeneity between studies was assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials that could not be ascribed to sampling variation (Higgins 2003) and by a Chi^2 test of the significance of the heterogeneity (Deeks 2001), irrespective of whether HRs or odds ratios (ORs) were calculated. If there was evidence of substantial heterogeneity, the possible reasons for this were investigated and reported.

Data synthesis

For meta-analysis of the time-to-event outcomes (OS and PFS), the most appropriate statistic is the HR. If provided in a trial report, the HR and associated variance were used directly in the meta-analysis. Alternatively, using the methods described in Parmar 1998, they were estimated indirectly from other summary statistics (95% confidence intervals (CI), P values, total number of events) or from data extracted from published Kaplan-Meier curves (Parmar 1998). Where feasible, a number of methods were used to estimate the trial HR indirectly, to check its reliability. The estimated HRs were then combined across all trials using the generic inverse variance facility in RevMan 5 software to give a pooled HR (RevMan 2011). This represents the overall risk of an event with surgery versus radiotherapy.

In some papers only overall rates of local and distant recurrence were presented rather than a time-to-event analysis of these events. Therefore, only an OR of the rates of recurrence could be calculated, with no account being taken of the time to recurrence or any censoring. Data for recurrence were extracted from the text and the OR calculated from the total number of patients and the observed number of recurrences in each arm. The ORs for individual trials were then combined across all trials. These ORs indicate the odds of a local or distant recurrence in the surgery arm versus the radiotherapy arm.

Chi^2 tests were also used to assess the consistency of effect across different subsets of trials and were referred to as Chi^2 test for interaction. Pooling of data was only done if there was no clinical heterogeneity and if there were outcomes that could be combined. In the absence of statistical heterogeneity, a fixed-effect model was used; if there was statistical heterogeneity a random-effects model was used. Where pooling was not appropriate, the results of eligible trials was discussed in a narrative form. Ideally the analysis was on an ITT basis.

In all tests of significance a two-sided P value is given.

Sensitivity analysis

If there was a major variation in the quality of studies, it was examined in a sensitivity analysis.

RESULTS

Description of studies

Results of the search

A MEDLINE search (Appendix 3) identified 453 hits. A similar EMBASE search was carried out (Appendix 4), which identified 174 studies and a CENTRAL search (Appendix 2) revealed 153 hits. Search of Group's Specialised Register and Non-Trials Database revealed 81 and 40 studies, respectively. Searches of the Web of Science did not add any studies. The reference lists were checked and the handsearching of journals and congress abstracts did not add any studies.

As it was known to us that only a small number, if any, of RCTs had been published, we also incorporated other types of studies in this review, that is prospective observational studies, case-control studies and studies with historic controls.

Forty-three possible eligible studies were retrieved for more detailed information. We found five RCTs (Landoni 1997; Morley 1976; Newton 1975; Piver 1988; Roddick 1971). Reasons for excluding were description of histology was not provided, short follow-up time (Roddick 1971), survival of patients with AC was not described separately (Morley 1976; Newton 1975), the studies was identified as not being RCTs (Morley 1976; Piver 1988). One RCT was found to meet the inclusion criteria (Landoni 1997).

Of the remaining 38 abstracts obtained, 25 studies were excluded for the following reasons: not AC, wrong FIGO stage, duplicate report about same study, only abstract available (Rabin 1984; Wei 2005), FIGO stage not described, different type of intervention, no detailed result information. This left a total of 12 non-RCTs that were considered for inclusion (Angel 1992; Baalbergen 2004; Berek 1981; Chen 1998; Eifel 1991; Hopkins 1988; Hurt 1977; Kilgore 1988; Kleine 1989; Nola 2005; Saigo 1986; Weiss 1986). Two studies reported data from the same department, but from different time periods. Eifel et al reported from 1965 to 1985 and Rutledge et al from 1947 to 1971, which overlapped by five years (Eifel 1991; Rutledge 1975). The five-year survival after surgery in stage IB in the Rutledge study was 33.3%, which is not in accordance to literature. Therefore we excluded the Rutledge study. After primary surgery, patients were irradiated in case of positive lymph nodes, compromised surgical margins, extension to parametrium. The indication for adjuvant therapy was not well described in some studies (Berek 1981; Hurt 1977; Nola 2005; Saigo 1986) as well as the percentage of patients who received adjuvant radiotherapy in Angel 1992 (12%), Baalbergen 2004 (21%), Chen 1998 (13%), Eifel 1991 (14%), Hopkins 1988 (14%), Hurt 1977 (0%), Kilgore 1988 (18%), Landoni 1997 (64%), Nola 2005 (not reported), Saigo 1986 (11%) and Weiss 1986 (55%).

All studies apart from the RCT (Landoni 1997) were retrospective and with a long time span of between nine (Weiss 1986) and 32 (Saigo 1986) years. The studies of Baalbergen 2004 and Saigo 1986 were multicentric but therapy was uniform. All the other studies were single centre.

Except for the RCT study (Landoni 1997), all other studies were retrospective cohort studies with variable methodological quality and limitations of a retrospective study. Comparing the results from these retrospective studies was not possible due to diverging treatment strategies. See QUOROM statement flow diagram (Table 1).

Subsequent searches (2012) identified in EMBASE 135 hits and in CENTRAL 172 hits. Search of Group's Specialised Register and Non-Trials Database revealed no new studies. Searches of the Web of Science did not add any studies. The reference lists were checked and the handsearching of journals and congress abstracts did not add any studies. Three studies seemed potentially relevant; of one only the abstract was available (Maneo 2011) and in two the results were not described by intervention (Bansal 2009; Galic 2012) (Figure 2).

For the most recent search 202 records were identified after preliminary de-duplication: CENTRAL N = 59, MEDLINE N = 53 and Embase N = 90. After title and abstract sifting 61 references remained and full text assessment identified three potentially relevant studies (Landoni 2017; Okadome 2020; Viani 2020).

Included studies

We found only one RCT (Landoni 1997), which is described in detail in Characteristics of included studies. This study was a prospective RCT of radiotherapy versus surgery in stage IB-IIA cervical cancer from 1986 to 1991, in patients referred to the Department of Obstetrics and Gynecology and Radiation Oncology at the Istituto di Scienze Biomediche S Gerardo, University of Milan. Of the 468 eligible patients, a high percentage, 27% (N = 125) were excluded because of age (N = 43), medical illness (N = 54), former or concurrent malignancy (N = 21), or doctors or patients preference for a primary therapy (N = 7). Women under 30 years of age were excluded, the mean age in the study was 50 years.

This study included 46 patients with AC. Twenty-six patients had primary surgery and 20 had primary radiotherapy. A relatively high percentage of the primary surgery patients had adjuvant radiotherapy (64%).

Primary surgery was uniform. Surgery consisted of a class III radical hysterectomy as described by Piver 1974. Adjuvant radiotherapy was given as a precaution for the following pathological risk factors: stage was greater than FIGO stage IIA, less than 3 mm of uninvolved cervical stroma, cut through or lymph node metastases. Adjuvant radiotherapy consisted of external pelvic irradiation, with a total dose of 50.4 Gy over five to six weeks. Sixty-four per cent (108 out of 170) of the surgery group received adjuvant radiotherapy, which is high compared to the percentages of 9% to 38% cited in literature (Morris 1994). For the 26 AC patients who had primary surgery and received adjuvant radiotherapy similar details were not provided.

Primary radiotherapy included external pelvic irradiation with 18 MV photon beam by a multi-portal technique. The median total dose was 47 Gy (range 40 to 53). After two weeks one caesium-137 LDR insertion was given. The median total dose at point A (external beam plus brachytherapy) was 76 Gy (range70 to 90).

When lymphangiography showed common iliac or para aortic metastases, para aortic lymph nodes were treated with a radiotherapy dose of 45 Gy over five weeks. A boost of 5 to 10 Gy was given to the positive lymph nodes. In the surgery group, lymphangiography revealed positive nodes in 24 patients (14%). Six of these 24 patients showed no lymph-node metastases in the surgical specimen. Whereas 27 of the 145 patients in the lymphangiography-negative surgery group also had nodal metastases. If nodal tumour metastases were discovered at the time of an attempted radical hysterectomy, some surgeons completed the radical hysterectomy while other surgeons abandoned it and patients were treated by radiotherapy. It was not described in this study how these patients were allocated, to the primary surgery or the primary radiotherapy group.

Median follow-up was 87 months (range 57 to 120). No patient was lost to follow-up. The outcomes assessed were the five-year survival, rate and pattern of complications, and recurrences associated with each primary therapy. Twenty year follow-up data available (Landoni 2017, in: Landoni 1997)

Excluded studies

We had planned to incorporate observational studies, case-control studies, non-randomised studies with concurrent controls and studies with historical controls in this review. We found 42 possible eligible studies but all these studies were of insufficient methodological quality, therefore we excluded all these 42 non-RCTs. See Characteristics of excluded studies.

Risk of bias in included studies

Allocation

In the Landoni study patients were randomly assigned radical surgery or radical radiotherapy (Landoni 1997). Patients were also stratified by cervical diameter. There was adequate sequence generation and allocation concealment (block randomisation from a computer-generated table in clusters of 10 cases of each stratum of cervical diameter).

Blinding

There was no blinding during treatment or follow-up surveillance.

Incomplete outcome data

After randomisation there were six protocol violations: two in the surgery group and four in the radiotherapy group. In 10 patients a treatment cross-over occurred. A total of 327patients received the scheduled treatment, 169 primary surgery and 158 primary radiotherapy. The median follow-up was 87 (range 57 to 120) months. No patient was lost to follow-up.

Selective reporting

To describe survival all patients with ITT were analysed. For the analysis of complications, 10 patients who had a treatment cross-over were excluded. A high percentage of patients (27%, N = 125) were excluded before randomisation due to age or medical illness.

Other potential sources of bias

The current staging procedure for cervical cancer (FIGO clinical staging system including imaging) is under discussion as it is a clinical pre-treatment staging. However, at the time of performing this study, it was, and still is, the standard tool of staging cervical cancer.

Effects of interventions

There was no survival benefit for either arm for all cervical cancer patients, but the multivariate (subgroup) analysis showed a marginally significant advantage in OS in the 46 AC patients after primary surgery compared to primary radiotherapy (OR 0.67; 95% CI 0.2 to 2.26; P = 0.05) (Analysis 1.1). OS was only just significantly better after primary surgery (70%) versus primary radiotherapy (59%). It is not clear if this minor difference could be explained by the average higher age of the radiotherapy group. The DFS was 66% after primary surgery and 47% after primary radiotherapy (OR 0.43; 95% CI 0.13 to 1.43; P = 0.02) (Analysis 2.1).

Most complications were described after combination therapy. In the surgery group (surgery only and surgery plus radiotherapy), 48 (28%) patients showed severe (grade 2 to 3) morbidity that required medical or surgical treatment, compared with 19 (12%) patients in the radiotherapy group (OR 3.32; 95% CI 0.61 to 18.12) (Analysis 1.2). After surgery only 16% of the patients had short-term morbidity and 24% had long-term morbidity. After surgery and adjuvant radiotherapy these percentages were 20% and 29%, respectively, and after radiotherapy alone were 7% and 16%, respectively. Owing to the high percentage of adjuvant radiotherapy after surgery, and as a result of combining treatment, the morbidity was relatively high in the surgery arm. The study gave the complication data for the whole group but not for AC separately.

DISCUSSION

Summary of main results

For early-stage AC surgery was better than radiotherapy. The majority of operated patients required adjuvant radiotherapy. Combined therapy (surgery and adjuvant radiotherapy) gave the highest complications and morbidity. The radiotherapy used in this study was not optimal.

Overall completeness and applicability of evidence

We have found only one RCT for this review. It included 46 patients with AC. The mean age of patients in the study was high (50 years) compared to that in other studies (43 to 47 years) (Chen 1998; Eifel 1991; Kilgore 1988; Nola 2005; Saigo 1986).

Because of the high percentage of patients excluded before randomisation due to age or medical illness, the results for this study apply only for relatively healthy patients in the age range 30 to 70 years.

The patients received a relatively low radiation dose (median dose: 76 Gy; range 70 to 90). According to the recommendation of the American Brachytherapy Society, the total dose to 'point A' in stage IB-IIA diseases should be in the range of 80 to 85 Gy (Nag 2002).

The study was performed from 1986 to 1991. At that time, it was not standard practice to combine chemotherapy with radiotherapy in the treatment cervical cancer patients. Since then, concurrent chemoradiation in either definitive or postoperative setting has been shown to be superior to radiotherapy alone (Green 2001; Green 2005; Peters 2000).

Quality of the evidence

The quantity and quality of the evidence was scarce and only one RCT was found (Landoni 1997), which included only 46 patients with AC from 337 cervical cancer patients.

AUTHORS' CONCLUSIONS

Implications for practice

Analysis of a subgroup of the single RCT showed that surgery for early-stage AC was better than radiotherapy. However, the majority of the surgery group patients required adjuvant radiotherapy, which was associated with greater morbidity. Furthermore, radiotherapy was not optimised and surgery was not compared to chemoradiation, which is currently recommended in most centres. Finally, modern imaging techniques (MRI, PET-CT), allow for better patient selection enabling node-negative patients to be more easily identified for surgery, thereby reducing the risk of morbidity associated with surgery and adjuvant radiotherapy.

In conclusion, we recommend surgery for early-stage AC of the uterine cervix in carefully staged patients. Whereas primary

chemoradiation remains a second best alternative for patients unfit for surgery and chemoradiation probably is first choice in patients with (MRI or PET-CT-suspected) positive lymph nodes. Twenty-year follow-up confirmed these results (Landoni 2017, in Landoni 1997).

Since the last version of this review no new studies were found.

Implications for research

There is a need for well-designed RCTs comparing primary surgery versus primary radiotherapy plus concurrent chemotherapy for early AC. This can only be carried out in women who do not need fertility-sparing treatment.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Landoni 1997

Study characteristics	
Methods	Randomised controlled trial 1986 to 1991; Milan, Italy
Participants	337 patients with stage IB or IIA cervical cancer: 46 with cervical adenocarcinoma
Interventions	Surgery consisted of a Class III radical abdominal hysterectomy n + 26. Adjuvant radiotherapy was given if at least 1 pathological risk factor (stage > pT2a, less than 3 mm uninvolved stroma, cut through, lymph-node metastases)

Landoni 1997 *(Continued)*

	Radiotherapy included external beam pelvic irradiation plus brachytherapy. Total dose at point A ranged 70 to 90 Gy (median 76 Gy) N = 20.
Outcomes	5-year overall survival: 70% after primary surgery (N = 26) versus 59% after primary radiotherapy (N = 20). No evidence of disease at 5 years: 66% after surgery versus 47% after radiotherapy Complications surgery-related 28%, radiation-related 12% For patients with cervical adenocarcinoma, the 20-year overall survival: 71% and 47% for surgery and radiotherapy respectively.
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) 5 yr survival	High risk	In the follow-up primary therapy was obvious
Blinding (performance bias and detection bias) complications	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Angel 1992	Retrospective study, 1966 to 1990, New York USA. 89 patients with stage I. Treatment prior to 1980 consisted mainly of radiotherapy and pre-operative radiotherapy, after 1980 the primary therapeutic approach was radical surgery
Attanoos 1995	Retrospective study, 1971 to 1990, Cardiff UK.55 patients. Survival was not described separately for stage and therapy
Baalbergen 2004	Retrospective study, 1989 to 1999, Rotterdam, Netherlands. 200 stage I and IIA patients. Patients had primary radiotherapy when their clinical condition was poor or because of old age

Study	Reason for exclusion
Bansal 2009	Retrospective study, 1988 to 2005, SEER database USA. Survival for different therapies for adenocarcinoma alone was not given separately
Berek 1981	Retrospective study, 1953 to 1978, UCLA USA. 48 stage IB patients. Reason for choice of primary therapy not given
Chargui 2006	Retrospective study, 1990 to 1999 Tunis. Patients with stage I and IIA had pre-operative radiotherapy 45 Gy followed by radical surgery (51 patients) or surgery and radiotherapy (1 patient)
Charkviani 1990	Retrospective study, 1964 to 1989, USSR. 98 patients. Survival not separately mentioned for AC
Chen 1998	Retrospective study, 1977 to 1994, Taipei Taiwan. 240 patients. Patients were encouraged to undergo surgical treatment instead of radiotherapy
Covens 1999	Retrospective study, 1984 to 1995, Toronto Canada. Study was only about surgery in early stage I AC
Eifel 1990	Retrospective study, 1965 to 1985, MD Anderson, USA. Different treatment for early stage was precisely described but survival was not given separately for primary surgery versus primary radiotherapy
Eifel 1991	Retrospective study, 1965 to 1985, MD Anderseon USA. 160 patients with an abnormal lymphography were treated with radiotherapy. Patients determined to have positive nodes at explorative surgery did not undergo planned hysterectomy but were given radiotherapy
Erzen 2002	Retrospective study, 1995 to 1999, Slovenia. Therapy (surgery versus radiotherapy) and outcome were not described separately
Farley 2003	Retrospective study, 1988 to 1999, Military Health Care System USA. Survival for different therapies was not given separately
Galic 2012	Retrospective study, 1988 to 2005, SEER database. Survival for different therapies was not given separately
Grigsby 1988	Retrospective study, 1959 to 1982, Washington USA, only about radiation
Hansen 1981	Prospective non-randomised study, 1974 to 1977, Odense, Denmark. Histology was not mentioned. Standard therapy was pre-operative radiotherapy followed by surgery. When a contraindication to operation was found patients had radiotherapy only
Hopkins 1988	Retrospective study, 1970 to 1985, Michigan USA. 125 stage I AC patients. Allocation for primary therapy not given
Hopkins 1991	Retrospective study, 1970 to 1985, Michigan USA. Only description of P value in a Cox Model Multiple Proportion Hazard Analysis for patients with stage IB AC according to treatment
Hurt 1977	Retrospective study, 1954 to 1974, Virginia USA. 20 stage I AC patients. Choice for primary therapy not described, only 3 had primary surgery
Ireland 1985	Retrospective study, 1969 to 1983, Gateshead, UK. Survival was not given separately for different treatment
Kemi 2014	This study in cervical cancer found no differences in survival, perhaps due to patient selection bias. Only for the adenocarcinoma in the surgery group, the 5 year survival was given, not for the adenocarcinoma in the radiotherapy group.

Study	Reason for exclusion
Kilgore 1988	Retrospective study, 1963 to 1985, Alabama USA. 130 stage I AC patients. Selection of treatment was not described
Kjorstad 1977	Retrospective study, 1963 to 1968, Oslo Norway. All patients had intracavitary radium treatment followed by surgery or radiotherapy
Kleine 1989	Retrospective study, 1964 to 1985, Freiburg Germany. 64 stage I patients. Clinical stage differentiation inadequate
Leminen 1990	Retrospective study, 1976 to 1980, Helsinki Finland. 63 patients. Surgery was pre-treated with a single intracavitary irradiation
Martel 2000	Case-control study, 1978 to 1992, Toulouse, France. Small numbers, survival was not separately given for different therapy per stage
Miller 1993	Retrospective study, 1964 to 1989, Memphis USA. Survival was not described for different therapies
Milsom 1983	Retrospective study, 1965 to 1974, Göteborg Sweden. Primary therapy consisted of intracavitary radiation followed by surgery or intracavitary plus external irradiation
Morley 1976	Retrospective study, 1945 to 1975, Michigan USA. Survival of patients with AC was not separately described
Newton 1975	Prospective study of surgery versus radiotherapy in cervical cancer, 1956 to 1966, Chicago USA. Survival of 7 patients with AC was not described separately
Nola 2005	Retrospective study, 1978 to 1998, Zagreb Croatia. 36 AC stage I-IV patients. Survival after primary surgery versus primary radiation was not subdivided for stage
Okadome 2020	This study is about bulky pTIIB cervical cancer; AC versus SCC. Not early cervical cancer.
Papanikolaou 2006	Retrospective study, 1993 to 2000, Greece. Therapy and survival for AC (only 11 patients) not separately described
Perez 1995	Retrospective study, 1966 to 1995, Missouri USA. Irradiation versus irradiation plus surgery in cervical cancer. Survival of AC patients is not separately described
Piver 1988	Retrospective study, 1974 to 1983, Buffalo USA. Treatment and survival of patients with AC was not separately described
Rabin 1984	South-African article from 1984. Study about radiotherapy plus surgery versus surgery in cervical cancer. In abstract no description of AC histology. Article could not be obtained
Roddick 1971	Randomised study, Kentucky USA, Surgery versus radiotherapy in cervical cancer. But no description of histology, no AC described, short follow-up
Rutledge 1975	Retrospective observational study, 1947 to 1971, MD Anderson USA. 61 stage I and IIA patients. 5-year-survival after surgery in stage IB was 33.3%; this is not according to literature
Saigo 1986	Retrospective study, 1949 to 1981, New York USA. 102 stage IB and IIA patients. Allocation for primary treatment not described. Wide variation in radiation treatment during the interval of this study
Shingleton 1981	Retrospective study, 1969 to 1980, Alabama USA. Survival is not separately described for different therapies. Same clinic as Kilgore 1988

Study	Reason for exclusion
Sundfor 1996	Randomised study, 1968 to 1980, Oslo Norway. Radiotherapy versus radiotherapy plus surgery in SCC
Townsend 1980	Randomised study, Melbourne. Intracavity radon followed by radical hysterectomy and pelvic lymph nodes versus intracavitary radon plus external megavoltage irradiation followed by extended hysterectomy in cancer of the cervix. Histology AC not described
Viani 2020	This study about survival in cervical cancer after different types of radiotherapy, not surgery vs radiotherapy. Only 22 % AC in this group.
Waldenström 1999	Retrospective study, 1987 to 1994, Göteborg Sweden. Survival was not separately described after primary surgery versus primary radiotherapy
Wei 2005	Retrospective study, 1970 to 2002, China. 105 AC patients. 5 year-survival for stage I 58%, which is not in accordance with literature. only abstract available
Weiss 1986	Retrospective study, 1970 to 1979, San Diego USA. 28 AC stage IB and IIA patients, < 4 cm. Treatment was based on stage of the lesion and the general medical condition of the patient
Yamashita 2005	Retrospective study, 1991 to 2004, Tokyo Japan. Surgery versus radiotherapy in cervical cancer. Survival of 24 patients with AC was not described separately

DATA AND ANALYSES

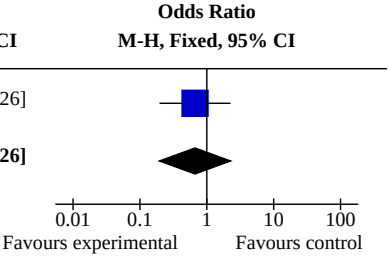
Comparison 1. Survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 5-year survival	1	46	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.20, 2.26]
1.2 Complications	1	46	Odds Ratio (M-H, Fixed, 95% CI)	3.32 [0.61, 18.12]

Analysis 1.1. Comparison 1: Survival, Outcome 1: 5-year survival

Study or Subgroup	Primary surgery Events	Total	primary radiotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Landoni 1997	8	26	8	20	100.0%	0.67 [0.20 , 2.26]
Total (95% CI)		**26**		**20**	**100.0%**	**0.67 [0.20 , 2.26]**
Total events:	8		8			

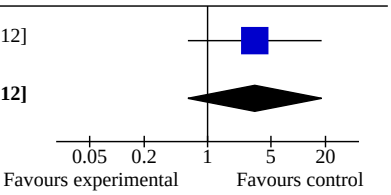
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Survival, Outcome 2: Complications

Study or Subgroup	Primary surgery Events	Total	Primary radiotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Landoni 1997	7	26	2	20	100.0%	3.32 [0.61 , 18.12]
Total (95% CI)		**26**		**20**	**100.0%**	**3.32 [0.61 , 18.12]**
Total events:	7		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)
Test for subgroup differences: Not applicable



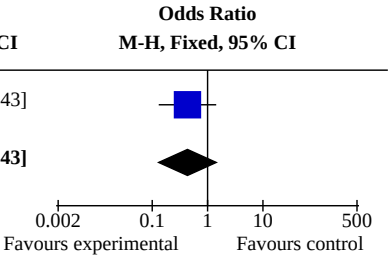
Comparison 2. Disease-free survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Disease-free survival	1	46	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.13, 1.43]

Analysis 2.1. Comparison 2: Disease-free survival, Outcome 1: Disease-free survival

Study or Subgroup	Primary surgery Events	Total	Primary radiotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Landoni 1997	9	26	11	20	100.0%	0.43 [0.13 , 1.43]
Total (95% CI)		**26**		**20**	**100.0%**	**0.43 [0.13 , 1.43]**
Total events:	9		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Data collection form

Intervention A	intervention B

Study identification: Form filled in by:
Reference checked by:
Date completing form:
Name study:
1st author, journal, year:
Study properties
RCT, non-randomised controlled study, CCT, observational study prospective/retrospective
Time of inclusion:
Purpose of the study, as stated by authors:
Selection bias
Performance bias
Attribution bias
Detection bias
Analysis (statistics)
Study eligible for review: yes / no

Table 1. Data collection form *(Continued)*

If not, why not:
Types of participants: Intervention A Intervention B
Number of patients:
Age:
Mean:
Median:
SD:
Ranges:
Primary tumours:
FIGOstage IA
IB-IIA
IIB-
Histological type
Adenocarcinoma
Adenosquamous
Other (specify)
Grade: I
II
III
unknown
Performance Status: WHO
Types of intervention:
Surgery planned
Conservative surgery
Radical surgery
Protocol violations
Radiationtherapy planned
-External & brachytherapy:
total Gy: fractions: frequency: field:
-Chemoradiation
total Gy: fractions: frequency: field:
CT agent(s) doses: frequency
Protocol violations
Surgery & Radiation therapy
-reason:
Outcome A B
Total patients entering the study
Declared ineligible
Removed from study for other reasons
Included in analysis
Completed prescribed treatment plan
(and available for response)
Follow up: A B
Known of .. patients.
Time of f.u. median:
SD:
Range:
Alive (5-yr survival)
Without evidence of disease
With disease
Death:
DOD
Treatment complications
Not related death
Unknown
Recurrence: yes / no
If yes time-interval (month)
If yes: local, distant, both
Complications:
-radiation-related
-surgery-related

Table 1. Data collection form *(Continued)*

-death

Table 2. Critical review form; randomised studies

yes - no
Did study population meet our criteria?
or: is it possible to analyse patients that meet our criteria separately?
Was assignment of patients to treatment randomised?
Were patients analysed in the groups to which they were randomised?
Were the groups similar at the start of the trial?
Aside from the experimental intervention, were the groups treated equally?
Were all patients who entered the trial accounted for at its conclusion?
How long was follow up? (Median and range)
Were interventions defined adequately?
Were all clinically important outcomes considered?
-disease free survival
-complications

Table 3. Critical review form; studies with non-randomised controls

yes - no
Did study population meet our criteria?
or: is it possible to analyse patients that meet our criteria separately?
Is the study adjusted for confounders?
Were patients analysed in the groups to which they were assigned?
Were the groups similar before treatment?
Aside from the experimental intervention, were the groups treated equally?
Are controls concurrent or retrospective?
Were all patients accounted for at the end of follow up?
How long was follow up?
Were interventions defined adequately?
How precise was the estimate of the treatment effect?
-disease free survival
-complications
Were all clinically important outcomes considered?
-disease free survival
-complications

Table 4. Critical review form; observational studies

yes - no
Did study population meet our criteria?
or: is it possible to analyse patients that meet our criteria separately?
Were all observed patients accounted for at the end of follow up?
How long was follow up?
Were interventions defined adequately?
Is the study cohort defined temporally?
Is the study cohort defined geographically?
Percentage of defined patient population who are included in the study?

Table 4. Critical review form; observational studies *(Continued)*

Were all clinically important outcomes considered?
-disease free survival
-complications

APPENDICES

Appendix 1. FIGO staging

FIGO Stage I

Carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded). Invasive carcinoma that can be diagnosed only by microscopy. All macroscopically visible lesions, even with superficial invasion, are allotted to Stage IB carcinomas. The involvement of vascular spaces, venous or lymphatic, should not change the stage allotment.

- IA_1 Measured stromal invasion of not more than 3.0 mm in depth and width of not more than 7.0 mm.
- IA_2 Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm with a width of not more than 7.0 mm.
- IB_1 Clinically visible lesions not more than 4.0 cm, or pre-clinical lesions greater than IA_2.
- IB_2 Clinically visible lesions more than 4.0 cm.

FIGO Stage II

Cervical carcinoma invades beyond the uterus, but not to the pelvic sidewall or to the lower third of the vagina.

- IIA1 No obvious parametrial involvement and tumour size of 4 cm or less with involvement of less than the upper two-thirds of the vagina.
- IIA2 No obvious parametrial involvement and tumour size of more than 4 cm with involvement of less than the upper two-thirds of the vagina (Pecorelli 2009).
- IIB Obvious parametrial involvement (Benedet 2001).

Appendix 2. CENTRAL search strategy

CENTRAL Issue 3 2009

#1 MeSH descriptor Uterine Cervical Neoplasms explode all trees
#2 MeSH descriptor Cervix Uteri explode all trees
#3 cervi*
#4 (#2 OR #3)
#5 cancer* or tumor* or tumour* or neoplas* or malignan* or carcinom* or adenocarcinom*
#6 MeSH descriptor Adenocarcinoma explode all trees
#7 MeSH descriptor Carcinoma, Adenosquamous explode all trees
#8 (#5 OR #6 OR #7)
#9 (#4 AND #8)
#10 (#1 OR #9)
#11 MeSH descriptor Gynecologic Surgical Procedures explode all trees
#12 surg*
#13 Any MeSH descriptor with qualifier: SU
#14 MeSH descriptor Hysterectomy explode all trees
#15 hysterectomy
#16 (#11 OR #12 OR #13 OR #14 OR #15)
#17 MeSH descriptor Radiotherapy explode all trees
#18 Any MeSH descriptor with qualifier: RT
#19 radiation
#20 brachytherapy
#21 chemoradi*
#22 radiochemo*
#23 (#17 OR #18 OR #19 OR #20 OR #21 OR #22)
#24 (#10 AND #16 AND #23)

Appendix 3. MEDLINE search strategy

MEDLINE Ovid 1950 to July week 5 2009

1 exp Uterine Cervical Neoplasms/
2 exp Cervix Uteri/ or cervi*.mp.
3 1 or 2
4 exp Adenocarcinoma/
5 adenocarcinoma*.mp.
6 exp Carcinoma, Adenosquamous/
7 adenosquamous carcinoma*.mp.
8 4 or 5 or 6 or 7
9 3 and 8
10 exp Gynecologic Surgical Procedures/
11 surg*.mp.
12 surgery.fs.
13 exp Hysterectomy/
14 hysterectomy.mp.
15 10 or 11 or 12 or 13 or 14
16 exp Radiotherapy/
17 radiotherap*.mp.
18 radiotherapy.fs.
19 radiation.mp.
20 brachytherapy.mp.
21 chemoradi*.mp.
22 radiochemo*.mp.
23 16 or 17 or 18 or 19 or 20 or 21 or 22
24 9 and 15 and 23
25 randomized controlled trial.pt.
26 controlled clinical trial.pt.
27 randomized.ab.
28 clinical trials as topic.sh.
29 randomly.ab.
30 trial.ti.
31 exp Cohort Studies/
32 cohort*.mp.
33 exp Case-Control Studies/
34 (case* and control*).mp.
35 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36 24 and 35
37 (animals not (humans and animals)).sh.
38 36 not 37

key:
mp=title, original title, abstract, name of substance word, subject heading word
fs=floating subheading
pt=publication type
ab=abstract
sh=subject heading

Appendix 4. EMBASE search strategy

EMBASE 1980 to 2009 week 32

1 exp uterine cervix tumor/
2 exp uterine cervix/ or cervi*.mp.
3 1 or 2
4 exp adenocarcinoma/
5 adenocarcinoma*.mp.
6 exp adenosquamous carcinoma/
7 adenosquamous carcinoma*.mp.
8 4 or 5 or 6 or 7
9 3 and 8

10 exp gynecologic surgery/
11 surg*.mp.
12 su.fs.
13 exp hysterectomy/
14 hysterectomy.mp.
15 10 or 11 or 12 or 13 or 14
16 exp radiotherapy/
17 radiotherap*.mp.
18 rt.fs.
19 radiation.mp.
20 brachytherapy.mp.
21 chemoradi*.mp.
22 radiochemo*.mp.
23 16 or 17 or 18 or 19 or 20 or 21 or 22
24 9 and 15 and 23
25 exp controlled clinical trial/
26 randomized.ab.
27 randomly.ab.
28 trial.ab.
29 groups.ab.
30 exp cohort analysis/
31 cohort*.mp.
32 exp case control study/
33 (case* and control*).mp.
34 exp retrospective study/
35 exp prospective study/
36 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37 24 and 36

key:
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name
fs=floating subheading
ab=abstract

Appendix 5. Cochrane Gynaecological Cancer Group's Specialised Register and Non-Trials Database

#8=CVX AND #11=SU AND #11=RT AND #12=TRT AND #4 <>ADVANCED AND #4 <>RECURRENT AND #4 <>REFRACTORY

WHAT'S NEW

Date	Event	Description
27 January 2021	Review declared as stable	No new studies identified in the latest search in 25 Novemeber 2020. Twenty year follow-update was found for the the one included study (Landoni 1997), which confirmed the findings of the original review. For women with cervical adenocarcinoma, the 20-year overall survival was 71% and 47% for surgery and radiotherapy respectively.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 1, 2010

Date	Event	Description
14 November 2012	Amended	Contact details amended

Date	Event	Description
7 November 2012	New citation required but conclusions have not changed	No new studies were identified for inclusion
7 November 2012	New search has been performed	A new search has been performed. The literature searches as described in the search strategy section were updated in June 2012.

CONTRIBUTIONS OF AUTHORS

AA and AB wrote the protocol. AB and YV did the search strategy, with help from Anne Oestmann and Jane Hayes of the Cochrane Gynaecological Cancer Review Group. AB and YV assessed eligibility of retrieved papers. AB prepared the initial text. AA advised on the methodology content and edited the text. LS searched for background material with special emphases on the radiotherapeutic subject and edited the text.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Other

External sources

- None, Other

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the Methods under the Types of studies we added "*The methodological quality of non-RCTs was assessed on the basis of comparability of treatment groups at baseline, adjustment for potential confounders and allocation of treatment".* We had not clearly stated this in the protocol. When we encountered the non-RCTs we found them on methodologically grounds (mainly due to selection of primary treatment) not qualified for our review, so that we excluded the non-RCTs.

As only one RCT was found to be suitable for inclusion the methods described in the Assessment of heterogeneity, Data synthesis and Sensitivity analysis were not used.

INDEX TERMS

Medical Subject Headings (MeSH)

Adenocarcinoma [drug therapy] [pathology] [*radiotherapy] [*surgery]; Carcinoma, Squamous Cell [pathology] [radiotherapy] [surgery]; Chemoradiotherapy; Combined Modality Therapy [methods]; Neoplasm Staging; Radiotherapy, Adjuvant [adverse effects]; Retrospective Studies; Uterine Cervical Neoplasms [drug therapy] [pathology] [*radiotherapy] [*surgery]

MeSH check words

Female; Humans