Management of women with stage IB2 cervical cancer with treatments other than chemoradiotherapy

A systematic review

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Management of women with stage IB2 cervical cancer with treatments other than chemoradiotherapy: a systematic review
was prepared and produced by:

Cancer Australia
Locked Bag 3 Strawberry Hills NSW 2012 Australia
Tel: +61 2 9357 9400 Fax: +61 2 9357 9477
Website: www.canceraustralia.gov.au

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Contributors

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See Appendix A for more information.

Executive summary

There are no national clinical practice guidelines regarding the management of women with stage IB2* cervical cancer in Australia. Members of the Gynaecological Cancer Advisory Group identified this as a key area, so Cancer Australia commissioned a systematic review of the research evidence about the management of women with stage IB2 cervical cancer.

Treatment options for stage IB2 cervical cancer include: primary radiotherapy/ chemoradiotherapy with or without adjuvant surgery; primary surgery with or without adjuvant therapy (radiotherapy/chemotherapy/chemoradiotherapy); or neoadjuvant chemotherapy followed by surgery.

While there are no Australian guidelines for the management of cervical cancer, in other international guidelines, concurrent chemoradiotherapy is most commonly recommended as the primary treatment for women with stage IB2 cervical cancer.[1-5] However, limited recommendations are available discussing other treatment options such as primary surgery or neoadjuvant chemotherapy. As the effectiveness of chemoradiotherapy compared with radiotherapy alone has been demonstrated in a number of randomised controlled trials (RCTs),[6] an expert multidisciplinary Working Group determined that the current systematic review would address the following research questions:

1. **What is the effectiveness of surgery in the management of women with stage IB2 cervical cancer?**

2. **What is the effectiveness of neoadjuvant chemotherapy in the treatment of women with stage IB2 cervical cancer?**

3. **What is the effectiveness of fertility preservation procedures in women with stage IB2 cervical cancer?**

In addition to the three primary research questions, the following two areas were also considered of interest by the Working Group and were included in the review, however these were investigated using targeted, non-systematic methods:

1. What is the effectiveness of investigative procedures in assessing stage to determine management of early-stage cervical cancer?

2. What is the influence of the length of time to treatment on outcomes for women with stage IB2 cervical cancer?

A search of the literature published between January 1998 and August 2013 was undertaken using electronic databases. The systematic review focused on stage IB2 cervical cancer, however many studies included broader populations, such as early or locally advanced cervical cancer, which included stage IB2 patients.

* FIGO Stage IB2 is defined as a clinically visible lesion >4cm in greatest dimension.

Over 140 papers were included in this review. The key results for each research question and area of interest are summarised below.

Surgery

Papers on the effectiveness of surgery were divided into four categories: primary surgery, trachelectomy, completion surgery (hysterectomy after radiotherapy/chemoradiotherapy), and different surgical methods for performing hysterectomy.

Fourteen studies,[7-22] including one randomised controlled trial (RCT),[7] were identified which investigated the use of primary surgery compared with primary radiotherapy/ chemoradiotherapy. The literature suggests that patients treated with primary surgery may have improved survival compared with primary radiotherapy/chemoradiotherapy, however results were inconsistent across studies. Recurrences appear to be more common in patients treated with radiotherapy, but differences were often not statistically significant. Adverse events were often not statistically significantly different between groups. No quality of life or fertility outcomes were reported in papers investigating primary surgery.

Only three comparative studies investigating trachelectomy in populations including stage IB2 cervical cancer were identified[23-25] (most studies on trachelectomy exclude tumours >2cm diameter). Of these studies, two were reported as abstracts only. No differences were reported between trachelectomy and hysterectomy for survival, recurrence, sexual dysfunction or quality of life. No fertility outcomes were reported in the comparative studies.

Seven studies,[26-33] including three RCTs,[26-29] were identified which investigated the addition of hysterectomy following primary radiotherapy/chemoradiotherapy (completion surgery). Completion surgery does not appear to offer any survival benefit compared with radiotherapy/chemoradiotherapy alone. Completion surgery may reduce the risk of recurrence (particularly distant metastases); however results were inconsistent between studies. No major differences in adverse events between groups were reported. Quality of life and fertility outcomes were not reported in any of the completion surgery studies.

Thirty-eight papers,[34-71] including five systematic reviews[34, 50, 62-64] and three RCTs,[49, 56, 59] were identified comparing different methods for performing radical hysterectomy. The most commonly reported comparisons were between open/abdominal radical hysterectomy, laparoscopic radical hysterectomy and/or robotic radical hysterectomy. Outcome data from the systematic reviews and RCTs were included in this review. Limited information on survival and recurrence were reported, although there was some indication that there is no difference in these outcomes between robotic and non-robotic methods for performing hysterectomy. Open/abdominal radical hysterectomy appears to have worse surgical outcomes (such as higher estimated blood loss and longer hospital stay) and adverse events than robotic hysterectomy. Most studies reported no significant difference in surgical outcomes between robotic and laparoscopic hysterectomy. One RCT reported that class II hysterectomy had shorter operation time than class III hysterectomy,[56] however no other differences in outcomes between these groups were reported. A small RCT reported superior surgical outcomes for laparoscopically assisted radical vaginal hysterectomy compared with open radical hysterectomy.[50]

Neoadjuvant chemotherapy

Four systematic reviews,[72-75] 11 RCTs[76-86] and 25 non-RCT comparative studies[14, 15, 19, 87-108] were identified which investigated neoadjuvant chemotherapy. Data from three of the

systematic reviews and RCTs not included in the reviews were included in this review. Papers were divided into two categories: neoadjuvant chemotherapy followed by local treatment compared with local treatment alone (note local treatment was usually surgery) and comparisons of different neoadjuvant chemotherapy regimens.

The systematic reviews and additional RCTs of neoadjuvant chemotherapy reported inconsistent results for survival. Individual trials reported no statistically significant differences between neoadjuvant chemotherapy and primary surgery groups.[76, 77] Pooled results reported in two systematic reviews indicated no statistically significant difference between neoadjuvant chemotherapy and primary surgery in one;[72] and a survival benefit following neoadjuvant chemotherapy in the other.[73] The third, older, systematic review by Tierney et al (2004)[74] reported that neoadjuvant chemotherapy tended to improve survival in trials using chemotherapy cycle lengths shorter than 14 days or cisplatin dose intensities greater than 25 mg/m^2 per week. In contrast, neoadjuvant chemotherapy led to poorer survival in trials using cycle lengths greater than 14 days or cisplatin dose intensities less than 25 mg/m^2 per week. In addition, neoadjuvant chemotherapy followed by surgery appeared to improve survival compared with exclusive radiotherapy. However significant heterogeneity was noted in both the design and results of the trials.

No statistically significant differences in rates of recurrence were reported between neoadjuvant chemotherapy and primary surgery groups. Patients receiving neoadjuvant chemotherapy were more likely to experience haematological toxicity. Neoadjuvant chemotherapy was also reported to reduce tumour size and reduce the need for adjuvant radiotherapy. No quality of life data were reported.

Two phase II RCTs compared the three-drug combination of paclitaxel/ifosfamide/cisplatin (TIP) with two-drug combinations ifosfamide/cisplatin (IP)[85] or paclitaxel/cisplatin (TP).[86] No survival difference was reported between the three-drug combination TIP and two-drug combination IP. Higher responses to neoadjuvant chemotherapy were observed with the three-drug combination, however this was also associated with more toxicity than either two-drug combination. No quality of life data were reported.

Fertility preservation

Thirteen papers[109-121] were identified on fertility preservation in populations thought to include stage IB2 cervical cancer (although percentages were often not reported). No comparative studies were identified, only small case series and surveys. It was noted that many other studies on trachelectomy were identified which excluded patients with tumours >2cm and which are therefore not included in this review. One paper demonstrated the feasibility of trachelectomy specifically in larger tumours (>2cm).[109] Successful full term pregnancies following trachelectomy have been reported in a number of papers; however rates of miscarriage were high in some studies. Two papers reported successful full term pregnancies following assisted conception after trachelectomy.[118, 121] Fertility concerns were common in women considering or undertaking trachelectomy. Following surgery, women were often concerned about recurrence, health of any future babies and pressure to conceive. No papers were identified on fertility outcomes following ovarian transposition in populations including stage IB2 cervical cancer.

Ongoing trials

A number of RCTs are currently being conducted in the management of stage IB2 cervical cancer, particularly comparing primary surgery or neoadjuvant chemotherapy with concurrent chemoradiotherapy. Results of these trials, which are not expected to be completed before 2018, are awaited with interest.

Conclusion

The majority of international guidelines recommended concurrent chemoradiotherapy as the primary treatment for stage IB2 cervical cancer (NCCN, ESMO, SIGN, ACR and CCO).[1-5] The NCCN and NICE guidelines also discuss radical hysterectomy as an option for primary treatment.[1, 122, 123] While NCCN does not recommend neoadjuvant chemotherapy,[1] ESMO note that neoadjuvant chemotherapy is an emerging area of investigation and appropriate indications have yet to be established.[2] No guideline recommendations were provided regarding the use of completion surgery, the ACR noted this was an area of investigation,[4] while the NCCN noted that the Panel disagreed regarding the use of completion surgery.[1]

Due to limitations with the evidence no assessment can be made regarding the relative effectiveness of primary surgery, or neoadjuvant chemotherapy followed by surgery, compared to chemoradiotherapy. Consequently, based on current available evidence it is difficult to determine if either primary surgery or neoadjuvant chemotherapy followed by surgery represent optimal treatment for stage 1B2 cervical cancer. Patient factors and patient/physician preference are likely to influence treatment choice. Results from ongoing trials may further guide management of these patients.

1 Introduction

1.1 Cervical cancer in Australia

In 2010, cervical cancer was the third most commonly diagnosed gynaecological cancer with 818 new cases in Australia, accounting for 1.6 per cent of all new cancers in women.[124, 125] In 2020, an estimated 915 Australian women are expected to be diagnosed with cervical cancer.[126]

The average age at diagnosis for cervical cancer is 51 years, the lowest average age of all of the gynaecological cancers.[127] Fifty-two per cent of women are less than 50 years old at diagnosis.[124]

1.2 Staging of cervical cancer

The International Federation of Gynecology and Obstetrics (FIGO) categorises cervical cancers by stages (revised staging 2009),[128] see Appendix B. Stage I cervical cancer is defined as being confined to the cervix.

FIGO stage IB2 is defined as a clinically visible lesion >4cm in greatest dimension. In the literature, this stage may be included within the definitions of early stage cervical cancer or bulky cervical cancer or, most commonly, locally advanced cervical cancer.

For the purposes of this review, the categorisations noted above have been included where stage IB2 is specifically included in the study population. Where possible, stratified results for women with stage IB2 cervical cancer have been reported. If stratified results are not available, overall results have been reported with the percentage of stage IB2 cervical cancers in the population noted.

1.3 Management of women with stage IB2 cervical cancer

Treatment options for stage IB2 cervical cancer include:

- primary radiotherapy/chemoradiotherapy with or without adjuvant surgery
- primary surgery with or without adjuvant therapy (radiotherapy/chemotherapy/ chemoradiotherapy) or
- neoadjuvant chemotherapy followed by surgery.

While there are no Australian guidelines for the management of cervical cancer, in other international guidelines, concurrent chemoradiotherapy is most commonly recommended as the primary treatment for women with stage IB2 cervical cancer.[1-5]

In 1999, the US National Clinical Institute issued an alert on cervical cancer that chemotherapy plus radiation improves survival based on the outcomes of five randomised trials.[129] More recently, a Cochrane systematic review summarised 15 randomised trials

comparing the use of chemoradiotherapy to radiotherapy in cervical cancer patients[6] and reported in a subgroup analysis (including 13 trials) that the survival benefit for chemoradiotherapy was greatest for patients with stage IA-2A cervical cancer compared with later stages (p=0.017).

Therefore chemoradiotherapy is the preferred treatment option compared with radiotherapy alone. However, limited recommendations are available discussing other treatment options such as primary surgery or neoadjuvant chemotherapy.

A recent Australian paper by Hacker et al (2013)[130] described the use of primary radical hysterectomy followed by tailored postoperative radiotherapy for treatment of stage IB2 cervical cancers. This paper describes their institutional preference to use this approach, regardless of tumour diameter or patient age. Of 106 stage IB2 cervical cancer patients treated from 1988 to 2008, 93 underwent primary surgical management and 13 had primary radiation therapy due to medical comorbidities, personal preferences or extensive associated vaginal intraepithelial neoplasia. The 93 primary surgery patients were retrospectively reviewed and the authors concluded that this method provided good survival with acceptably low morbidity.

As there are no national clinical practice guidelines about the management of women with stage IB2 cervical cancer in Australia, and members of the Gynaecological Cancer Advisory Group identified this as a key area, Cancer Australia commissioned a systematic review of the research evidence. As the effectiveness of chemoradiotherapy compared with radiotherapy alone has already been demonstrated in a number of RCTs, the multidisciplinary working group determined that the topics of most interest to investigate were other techniques, particularly the use of surgery and neoadjuvant chemotherapy in women with stage IB2 cervical cancer. In addition, the use of fertility preservation methods in these women was considered of interest.

2 Methods

The objective of this review is to investigate the management of women with stage IB2 cervical cancer.

Research questions addressed in this systematic review were:

1. **What is the effectiveness of surgery in the management of women with stage IB2 cervical cancer?**

2. **What is the effectiveness of neoadjuvant chemotherapy in the treatment of women with stage IB2 cervical cancer?**

3. **What is the effectiveness of fertility preservation procedures in women with stage IB2 cervical cancer?**

Additional areas of interest considered were:

1. What is the effectiveness of investigative procedures in assessing stage to determine management of early-stage cervical cancer?

2. What is the influence of the length of time to treatment on outcomes for women with stage IB2 cervical cancer?

These additional areas were investigated using non-systematic methods. Consequently, a summary of the evidence for these additional topics is not included in the main body of this systematic review, but is included as Appendix F.

The management of cervical cancer for women who are pregnant was outside the scope of the review and is not included.

2.1 Inclusion criteria

For all research questions and areas of interest:

- The study populations had to include stage IB2 cervical cancer patients. Studies including less than 10% stage IB2 patients were excluded (except for Additional Area 1 on investigative procedures, where smaller percentages were included).

- Studies with the following characteristics were excluded:
    - published prior to 1998
    - published exclusively in a language other than English
    - case studies, letters, opinion pieces, non-systematic/narrative reviews, patterns of care studies
    - comparisons between histological subtypes.

Specific details on inclusion and exclusion criteria for each research question and areas of interest are below. For PICO criteria for each research question and each additional area of interest please see Appendix C.

Research Question 1 - surgery in the management of women with stage IB2 cervical cancer

This research question included studies comparing the following interventions:

- **primary surgery:** surgery as initial treatment (with or without adjuvant therapy) compared with radiotherapy or chemoradiotherapy as initial treatment;
- **trachelectomy:** radical trachelectomy compared with radical hysterectomy;
- **completion surgery:** the use of hysterectomy after primary radiotherapy/ chemoradiotherapy (also known as adjuvant hysterectomy) compared with radiotherapy/chemoradiotherapy alone;
- **different surgical methods for performing hysterectomy:** comparisons between different methods such as, but not limited to, open (abdominal) radical hysterectomy, laparoscopic hysterectomy, and robotic hysterectomy.

Outcomes of interest were: overall survival, disease/progression-free survival, recurrence, quality of life/adverse events/toxicity, fertility outcomes.

The following studies were excluded:

- non-comparative studies
- studies investigating learning curves for surgeons to perform surgery
- studies investigating completed compared with aborted hysterectomy
- comparisons of incision methods or detailed level of surgery such as extent of pelvic lymphadenectomy.

Research Question 2 – neoadjuvant chemotherapy in the treatment of women with stage IB2 cervical cancer

This research question included studies comparing the following interventions:

- neoadjuvant chemotherapy followed by surgery compared with surgery alone
- neoadjuvant chemotherapy followed by surgery compared with exclusive radiotherapy/chemotherapy/chemoradiotherapy
- comparisons of different neoadjuvant chemotherapy regimens.

Outcomes of interest were: overall survival, disease/progression-free survival, response to chemotherapy, recurrence, quality of life/adverse events/toxicity.

The following studies were excluded:

- non-comparative studies
- studies investigating neoadjuvant radiotherapy or comparing neoadjuvant chemotherapy with neoadjuvant chemoradiotherapy.

Research Question 3 – fertility preservation procedures for women with stage IB2 cervical cancer

This research question included:

- comparative studies and case series reporting obstetric outcomes following fertility/ovarian preservation for stage IB2 cervical cancer patients
- fertility ovarian preservation procedures included trachelectomy, ovarian transposition, ovarian transplantation and ovarian cryopreservation.

Outcomes of interest were: successful full term pregnancy, adverse events, quality of life/psychosocial outcomes.

The following studies were excluded:

- management of patients who were already pregnant at time of cervical cancer diagnosis
- papers describing access to fertility preservation procedures
- papers solely reporting on the following outcomes:
    - preservation of ovarian function primarily to avoid the onset of menopausal symptoms rather than to preserve fertility
    - rate of ovarian metastases following treatment with radical hysterectomy and ovarian preservation.

Additional Areas

1 – investigative procedures for staging cervical cancer to determine management

Articles considered relevant included:

- studies reporting on use of pre-treatment investigative procedures to stage cervical cancer and/or to assign treatment.

Outcomes of interest were: improved accuracy of staging, treatment decisions

The following studies were excluded:

- studies investigating the use of post-treatment imaging to determine response to treatment
- papers solely reporting on the use of investigative procedures to identify lymph node metastases or parametrial invasion.

2 – influence of time to treatment

Articles considered relevant included:

- studies reporting on the effect of time to treatment for cervical cancer.

Outcomes of interest were: overall survival, disease/progression-free survival, quality of life/adverse events/toxicity, psychosocial outcomes.

The following studies were excluded:

- modelling studies
- general prognostic studies (ie not specifically focused on time to treatment).

2.2 Literature search

Search strategy

Literature searches were conducted in August 2013 to identify relevant studies which addressed the inclusion criteria. The searches were conducted using the following electronic databases:

- PubMed
- Embase
- Medline
- Cochrane Library.

One main search was conducted for the first two research questions, with a secondary search conducted for the third research question.

Papers addressing the two additional areas of interest were identified within the literature search results for the three research questions. Additional, focused, non-systematic literature searches for these areas were conducted using key papers identified in the main searches.

All searches were limited to studies conducted in humans and published in the English language since January 1998.

Reference lists of key articles were hand-searched to identify further relevant articles.

In addition, electronic databases of conference proceedings were searched from the following meetings from 2008 onwards:

- American Society of Clinical Oncology (ASCO) annual meeting
- International Gynecologic Cancer Society (IGCS) biennial meeting.

Search terms

The search terms used in the various search strategies are described in Table 1. The search strategies differed slightly for each electronic database, as appropriate. The main search strategy, developed with input from a multidisciplinary working group, combined terms which described stage IB2 cervical cancer with terms describing surgery and neoadjuvant chemotherapy, as well as the study types included. The secondary search strategy for the research question on fertility preservation used cervical cancer and fertility preservation terms but did not use stage-specific or study design terms, as agreed with the working group. Extra, non-systematic searches were conducted to identify further articles for the additional areas of interest using cervical cancer terms along with staging, treatment decisions and time-to-treatment terms.

Table 1 Search strategy terms

Topic	Terms used
Cervical cancer	Uterine Cervical Neoplasms/ or ((cervical or cervix) adj3 (cancer* or carcinoma* or tumor* or tumour* or adenocarcinoma* or neoplas*))
Stage IB2	"early stage" or "early disease" or "stage 1" or "stage I" or "stage 1B*" or "stage IB*" or "early cervi*" or 1B2 or IB2 or "locally advanced" or bulky
Surgery	gynecologic surgical procedure/ or (surgery or surgical or surgeries or hysterectomy or trachelectomy).ab,ti. or hysterectomy/
Neoadjuvant chemotherapy	chemotherapy/ or drug therapy/ or neoadjuvant therapy/ or chemotherap*.ab,ti.
Radiotherapy/chemoradiotherapy	radiotherapy/ or (radiotherap* or radiation or brachytherapy or chemoradi* or radiochemo*).ab,ti.
Fertility preservation	Fertility Preservation/ or 'fertility preservation' or 'preserve fertility' or ((ovary or ovaries or ovarian or embryo or embryonic or oocyte) and (transposition or transplant* or cryopreservation or 'cryo-preservation')) or ((reproduct* or fertility or ovary or ovarian) and preserv*)
Study type	"meta analysis" or "meta-analysis" or (systematic* and (review or search)) or guideline or "clinical recommendation" or "practice recommendation" or (random* or trial or cohort* or groups).ab,ti. or randomized controlled trial/ or controlled clinical trial/ or cohort studies/ or prospective studies/or retrospective studies/ or cohort analysis/
Staging[+]	*Neoplasm staging/
Treatment decisions[+]	*Decision making/ or "treatment decisions"
Time to treatment[+]	Time-to-treatment/ or *Time factors/ or "time to treatment" or "treatment delay" or "delay treatment" or ("wait time" or "waiting time" and treatment)

[+]implemented using a non-systematic approach to identify articles relevant for additional areas of interest, not part of main or secondary search

Type of studies

For each research question, the following types of studies were included: systematic reviews, meta-analyses, randomised controlled trials and pseudo-randomised control trials, as well as other comparative observational studies, including prospective and retrospective cohort studies, case-control studies and cross-sectional studies. Research question 3 also includes case series due to the limited number of comparative studies identified for this question. Additional area 1 included diagnostic studies and Additional area 2 included case series. Case studies, letters, opinion pieces and non-systematic reviews were excluded.

Guidelines/Clinical trials websites

In addition to the published literature, the following guideline and clinical trial websites were searched for relevant information about current international standards and ongoing areas of research about the management of stage IB2 cervical cancer:

- Cancer Care Ontario (CCO) (Canada) http://www.cancercare.on.ca/
- European Society of Medical Oncology (ESMO) http://www.esmo.org/
- Guidelines International Network (GIN) http://www.g-i-n.net/
- National Comprehensive Cancer Network (NCCN) (US) http://www.nccn.org/index.asp
- National Guideline Clearinghouse (NGC) (US) http://www.guideline.gov/
- National Institute for Health and Clinical Excellence (NICE) (UK) http://www.nice.org.uk/
- Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/
- Current Controlled Trials http://www.controlledtrials.com
- WHO International Clinical Trials Registry Platform http://apps.who.int/trialsearch/

The clinical practice guidelines and clinical trials website searches identified nine clinical practice guidelines and 10 ongoing clinical trials of interest.

Search results

Titles and abstracts identified by the literature searches were assessed independently by two reviewers for inclusion. Full text papers of potentially relevant citations were retrieved and assessed independently by two reviewers for inclusion. Any discrepancies were discussed and resolved between the reviewers with assistance from the Working Group, if necessary. Conference abstracts and articles for the additional areas on investigative procedures for staging and time to treatment were assessed for inclusion by one reviewer.

The main search identified 1607 citations, of which 223 citations were considered relevant for the first two research questions and were sourced for full text review. Eight citations were unable to have the full text sourced; therefore abstracts were used as relevant for the research questions. Within the main search, an additional 35 articles were considered

relevant for the third research question, 107 for Additional area 1, and two for Additional area 2.

The supplementary search identified 747 citations for Research question 3. One hundred and forty-three citations were sourced for full text review (including those identified in the main search). One abstract was identified in this search as relevant for Research question 1.

The non-systematic targeted searches identified 10 potentially relevant citations for Additional area 1 and five citations for Additional area 2.

The review of conference proceedings identified a further 24 abstracts of interest, however many of these had been superseded by full text papers identified in the literature searches. In one case an additional RCT was identified for inclusion.

Following full text review, sourcing additional papers from reference lists, cross-checking conference proceedings and completing non-systematic literature searches for the additional areas of interest the following were included:

- 65 citations for Research question 1 (16 on primary surgery, three on trachelectomy, eight on completion surgery and 38 on different surgical methods for performing hysterectomy)
- 40 citations for Research question 2 (primary data extracted from three systematic reviews and four RCTs)
- 13 citations for Research question 3
- 22 citations for Additional area 1
- 2 citations for Additional area 2
- 8 additional citations addressing other topics.

Note some citations identified were relevant for multiple research questions and/or additional areas. Please see Appendix D for the flowchart of the inclusion/exclusion process.

Data extraction

Data extraction was completed by one reviewer and verified by a second reviewer for accuracy. Where multiple citations were identified for one study, data was extracted from the most recent citation and full text papers when available. In some cases, more than one citation per study was used, if additional information on outcomes of interest were provided.

Descriptive data extracted from the studies included characteristics such as population, interventions and primary outcomes. Outcome data, including overall survival, progression-free/disease-free, quality of life (QoL) and adverse events, extracted from the studies varied between research questions.

Data is ordered in tables by study design (systematic review, RCTs, prospective studies, retrospective studies), followed by year. Where results are reported from multiple citations for the same study, these are presented together.

Quality assessment

Quality assessment was performed for systematic reviews and comparative studies using criteria based on NHMRC guidance.[131] Reviews and studies were assessed as being of high, medium or low quality.

For systematic reviews the following items were considered:

- whether an adequate search strategy and appropriate inclusion criteria were used,
- whether quality assessment was performed
- whether results were summarised and data pooled appropriately; and
- whether any heterogeneity was explored.

For comparative studies the following items were considered:

- the method of treatment assignment and minimisation of selection bias,
- whether outcome assessment was standardised,
- whether baseline characteristics were balanced between groups; and
- whether the study was adequately powered to detect differences in the outcomes investigated.

3 Results

3.1 International guidelines and recommendations

Currently, there are no Australian clinical practice guidelines which provide recommendations regarding the management of stage 1B2 cervical cancer.

Three international guidelines were identified which provide guidance on the management of cervical cancer in general, with sections relating to different stages of cervical cancer (US National Comprehensive Cancer Network (NCCN),[1] European Society of Medical Oncology (ESMO),[2] and Scottish Intercollegiate Guidelines Network (SIGN)[3]). Two guidelines specifically on early-stage cervical cancer were identified (American College of Radiology (ACR),[4] UK National Institute for Health and Clinical Excellence (NICE)[122]). One guideline was identified specifically on chemoradiotherapy for locally advanced cervical cancer (Cancer Care Ontario (CCO)[5]). One guideline on fertility preservation and cancer was identified (American Society of Clinical Oncology (ASCO)[132]). Two guidelines specifically on pre-treatment planning and staging of cervical cancer were also identified (ACR,[133] European Society of Urogenital Radiology)[134]).

Most of the identified guidelines recommended concurrent chemoradiotherapy as the primary treatment for stage IB2 cervical cancer (NCCN, ESMO, SIGN, ACR and CCO).[1-5] However, NCCN and NICE also discuss radical hysterectomy as an option for primary treatment.[1, 122, 123] While NCCN does not recommend neoadjuvant chemotherapy,[1] ESMO note that neoadjuvant chemotherapy is an emerging area of investigation and appropriate indications have yet to be established.[2] No guideline recommendations were provided regarding the use of completion surgery, the ACR noted this was an area of investigation,[4] while the NCCN noted that the Panel disagreed regarding the use of completion surgery.[1]

Relevant recommendations from these guidelines are provided in Appendix E. The guidelines about staging of cervical cancer are described in Section 3.5.1.

3.2 Surgery for management of women with stage IB2 cervical cancer

Summary of included papers

Included papers have been divided into the following subgroups:

- **3.2.1 Primary surgery:** studies investigating surgery as initial treatment (with or without adjuvant therapy) compared with radiotherapy or chemoradiotherapy as initial treatment.
- **3.2.2 Trachelectomy:** studies investigating radical trachelectomy compared with radical hysterectomy.

- **3.2.3 Completion surgery:** studies investigating the use of hysterectomy after primary radiotherapy/chemoradiotherapy (also known as adjuvant hysterectomy) compared with radiotherapy/chemoradiotherapy alone.

- **3.2.4 Different surgical methods for performing hysterectomy:** studies investigating comparisons between different methods such as, but not limited to, open (abdominal) radical hysterectomy, laparoscopic hysterectomy, and robotic hysterectomy.

3.2.1 Primary surgery

Sixteen citations were identified which compared primary surgery with primary radiotherapy/chemoradiotherapy to treat early/locally advanced cervical cancer. The citations included:

- One RCT comparing radical surgery to external radiotherapy plus brachyradiotherapy, reported in an abstract[7] and within one systematic review.[135] The review on primary surgery for early adenocarcinoma of the uterine cervix included only one RCT, which was a subset of the same RCT reported by Maneo et al (2011).[7]
- Thirteen retrospective studies[8-22] comparing surgery with radiotherapy alone or concurrent chemoradiotherapy.

Quality assessment

The systematic review was considered to be of high quality; however it only included one study. The RCT was reported in an abstract only therefore not enough detail was provided to assess quality. The majority of observational studies included were considered medium quality, some low-medium, mainly due to imbalances between groups at baseline. Primary radiotherapy groups were often older and more likely to have worse performance status and/or prognostic factors than primary surgery groups.

Study characteristics

Characteristics of the primary surgery studies are provided in Table 2. Seven studies did not report the percentage of stage IB2 patients included in the study.[7, 8, 13, 16, 20-22, 135] Four studies included only stage IB2 patients[11, 12, 15, 18, 19] and an additional study included >75% stage IB2 patients.[9] The population of the remaining two studies included <25% stage IB2 patients.[14, 17]

Primary surgery consisted of radical hysterectomy in most of the studies. One study did not explicitly state what surgery was performed, however radical hysterectomy was implied,[11] and two studies included a small percentage of patients receiving surgery other than radical hysterectomy.[13, 21]

Many patients in the primary surgery arms were treated with adjuvant radiotherapy/ chemoradiotherapy. One study stratified results by those receiving primary surgery only, primary surgery plus adjuvant radiotherapy/chemoradiotherapy and those receiving primary radiotherapy/chemoradiotherapy.[13]

The majority of patients in the included studies had squamous cell carcinoma. The mean age of patients was usually between 45 and 50 years old. In most of the retrospective studies, patients in the primary radiotherapy/chemoradiotherapy groups were significantly older than those in the primary surgery groups.[13-15, 19-21]

Patient selection criteria

Detailed information on patient selection criteria was not available due to the retrospective nature of nearly all of the studies. The RCT was reported in an abstract only therefore detailed patient selection criteria was not available for this trial.

In the retrospective studies, patients in the primary radiotherapy/chemoradiotherapy groups tended to be older and have worse performance status and/or prognostic factors.

Table 2 Characteristics of studies comparing primary surgery with primary radiotherapy/chemoradiotherapy for stage IB2 cervical cancer

Study	Population	Intervention	Control	Outcomes	Quality
Maneo 2011[7] RCT, abstract	Stage IB-IIA cervical cancer N=327 IB2: not stated	Radical surgery (n=169)	External RT plus BRT (n=158)	20y OS, relapses, recurrences	Unable to be assessed
Baalbergen 2013[135] Systematic review Includes 1 RCT (subset of RCT reported by Maneo 2011)	Cervical adenocarcinoma (stage IA-IIB) N=46 IB2: not stated	Primary surgery (RH) (n=26)	Primary RT (n=20)	5y OS, DFS, adverse events, QoL	High (Cochrane review)
Dickson 2012[8] Retrospective cohort, abstract	Stage IB-IV cervical cancer N=81 47% stage IB; IB2: not stated	Extra peritoneal lymph node dissection +/- external beam RT (n=50)	Intensity modulated radiation therapy (n=31)	OS, PFS, complications	Low/medium
Park 2012[9] Retrospective cohort M/C	IB2 and IIA2 cervical cancer N=215 IB2: 75-78%	RH followed by adjuvant therapy (n=147)	Primary CRT (n=68)	OS, PFS, complications	Medium
Rungruang 2012[11] Retrospective cohort M/C	Stage IB2 cervical cancer N=770 IB2: 100%	Primary surgery (n=401) +/- adjuvant RT	Primary radiation (n=369) +/- adjuvant surgery	OS, DFS	Medium
Courtney-Brooks 2010*[12] Retrospective cohort M/C, abstract	Stage IB2 cervical cancer N=780 IB2: 100%	Primary surgery (n=513)	Primary radiation (n=267)	OS	Medium
Yin 2011[14] Retrospective cohort S/C	Locally advanced cervical cancer (stage IB2-IIB) N=476 IB2: 15-31%	Radical surgery (hysterectomy plus pelvic lymph node dissection) (n=195)	Concurrent CRT (n=94)	OS, DFS, toxicity, complications, adverse events	Medium

Study	Population	Intervention	Control	Outcomes	Quality
Chen 2011[13] Retrospective cohort M/C	Stage IB1-IIA cervical adenocarcinoma N=258 Majority stage I; IB2: not stated	i) Radical surgery (n=174) ii) Radical surgery plus adjuvant RT or concurrent CRT (n=46)	RT or concurrent CRT (n=38)	OS, DFI	Medium
Turan 2010[15] Retrospective cohort S/C	Stage IB2 cervical cancer N=86+ IB2: 100%	RH (n=18)	RT (n=20)	OS, DFS, toxicity	Low/medium
Bansal 2009[16] Retrospective cohort, abstract	Early stage cervical cancer (IB-IIA) N=4885 IB2: not stated	RH (n=4012)	RT (n=873)	Survival	Low/medium
Kim 2009[17] Retrospective cohort S/C	Stage IB1-IIa SCC of cervix and suspicious para-aortic lymph node metastasis by preoperative CT & MRI N=54 IB2: 25%	RH followed by concurrent CRT (n=48)	Primary concurrent CRT (n=16)	OS, PFS, complications	Medium
Zivanovic 2008[18] Retrospective cohort S/C	Stage IB2 cervical cancer N=47 IB2: 100%	RH (n=27)	RT/CRT (n=20)	OS, PFS, recurrence, complications	Medium
Ryu 2007[19] Retrospective cohort M/C	Stage IB2 cervical cancer N=692+ IB2: 100%	Primary hysterectomy (alone (n=103) or with adjuvant RT or CRT (n=201))	Primary RT (n=48) or concurrent CRT (n=51); Completion surgery (after CRT (n=1) or after RT (n=6))	OS, DFS	Low/medium
Yamashita 2005[20] Retrospective cohort S/C	Stage I-II cervical carcinoma N=152 ~30% stage IB; IB2: not stated	Total or radical hysterectomy (n=115)	RT (n=37)	OS, CSS, complications	Medium

Study	Population	Intervention	Control	Outcomes	Quality
Macleod 2003[21] Retrospective cohort S/C	Early stage cervical cancer (IB and IIA) N=127 IB2: not stated	Surgery and adjuvant RT (n=81)	Definitive RT (n=46)	OS, RFS, local control, toxicity	Medium
Lin 1998[22] Retrospective cohort S/C	Cervical cancer (IB or IIA) N=85 IB2: not stated	RH alone (n=42) or followed by pelvic irradiation (n=15)	Pelvic irradiation (n=11)	Urodynamic findings	Low/medium

*Although this abstract reports different patient numbers than Rungruang 2012, study investigators were the same and patients were included from the same database over the same time period therefore outcome data is included from the full text Rungruang 2012 paper only to avoid duplication. +Patient numbers total more than the study arms as these studies included a third study arm investigating neoadjuvant chemotherapy which is not included in this section.

BRT=brachyradiotherapy; CRT=chemoradiotherapy; CSS=cause-specific survival; CT=computed tomography; DFI=disease-free interval; DFS=disease-free survival; M/C=multicentre; MRI=magnetic resonance imaging; OS=overall survival; PFS=progression-free survival; QoL=quality of life; RCT=randomised controlled trial; RFS=relapse-free survival; RH=radical hysterectomy; RT=radiotherapy; S/C=single centre; SCC=squamous cell carcinoma

Survival

Overall survival

Twelve studies reported on overall survival. Results for the impact of primary surgery on overall survival reported from the studies were inconsistent, see Table 3.

Six studies reported no significant differences in overall survival between those who received primary surgery with those receiving primary radiotherapy or chemoradiotherapy.[7, 15, 17-20, 135] This includes long-term follow-up data (reported in abstract only) from an RCT comparing primary surgery to primary radiotherapy in stage IB-IIA cervical cancer (% IB2 not stated) with 20 year overall survival rates of 72% in the surgery arm versus 77% in the radiotherapy arm (p=0.28).[7] On a multivariate analysis this study noted that type of treatment was not a significant factor for survival with the only risk factors being histotype (epidermoid tumours) (p=0.02), tumour diameter (>3cm) (p=0.008) and lymph node status (p<0.001). A subset of this RCT which included only cervical adenocarcinoma, was included in the systematic review by Baalbergen et al (2013) reported overall survival rates of 70% in the primary surgery arm versus 59% in the primary radiotherapy/chemoradiotherapy arm (OR 0.67; 95% CI 0.2, 2.26; p=0.05).[135]

The other studies reporting no significant overall survival differences were retrospective cohorts with median follow-up ranging from 2.6 to 10 years. The percentage of stage IB2 patients included in the study populations was 100% in three studies,[15, 18, 19] 25% in one study[17] and not stated in one study.[20] In the three studies including only stage IB2 cervical cancer patients, overall survival was superior in the primary surgery groups, however this was not statistically significant.[15, 18, 19] One of these stage IB2 studies, Ryu et al (2007),[19] described 10-year survival data. Radical hysterectomy appeared to have the best 10 year survival, followed by chemoradiotherapy, then neoadjuvant chemotherapy, with the radiotherapy alone group having the poorest survival.[19] However, further details, including statistical significance, were not provided.

Six studies reported a statistically significant improvement in overall survival for patients treated with primary surgery compared with primary radiotherapy or chemoradiotherapy.[9, 11, 13, 14, 16, 21] All studies were retrospective cohorts with median follow-up ranging from 3.3 to 6.9 years (not stated in two studies). The percentage of stage IB2 patients included in the study populations was 100% in the Rungruang et al study[11], >75% in the Park et al study[9], 22% in Yin et al study[14] and not stated in three studies.[13, 16, 21] One large retrospective study reported radical hysterectomy improved survival for tumours 4-6cm (HR 0.51; 95% CI 0.36, 0.72) compared with primary radiotherapy, but this improvement was not observed for tumours greater than 6cm.[16]

Selection bias might account for improvements in overall survival for patients treated with primary surgery. In the retrospective studies, patients receiving primary radiotherapy/ chemoradiotherapy tended to be older and were more likely to have larger tumours or worse performance status than those receiving primary surgery.[11, 13, 14, 21] MacLeod et al (2003) reported that more patients in the primary radiotherapy group died of other causes (37% vs 7%, p=0.0007) reflecting adverse factors such as older age and worse performance status in this group.[21] However, Rungruang et al (2012)[11] reported that differences for overall

and disease-free survival remained statistically significant when stratified by age, race and tumour size, although this study did note that survival was much lower for patients <25yrs at diagnosis. Similarly, when Yin et al (2011)[14] performed multivariate Cox regression models adjusted for statistically significant prognostic factors for OS and DFS, and overall survival appeared superior in the surgical group than the chemoradiotherapy group however details regarding direct comparison were not provided.

Progression-free/Disease-free survival

Nine studies reported on progression-free, disease-free or relapse-free survival, see Table 3. Three studies showed no significant difference between groups for progression-free[15, 18] or relapse-free[21] survival. The remaining six studies showed statistically significant improvements in progression-free,[17] relapse-free[9] or disease-free survival for those treated with primary surgery.[11, 13, 14, 135] The study by Kim et al (2009)[17] conducted a multivariate analysis for prognostic factors affecting PFS and found that the treatment type (surgery followed by adjuvant chemoradiotherapy) and stage IB1 were statistically significant factors for improved PFS, however stage IB2 was not statistically significant.

Mortality

Five studies reported the total number of deaths (from all causes) in each treatment group. One study reported that significantly fewer deaths occurred in patients treated with surgery than primary radiotherapy/chemoradiotherapy.[13] Three studies reported lower percentages of deaths in the surgery groups than radiotherapy groups but did not report statistical significance.[14, 15, 20] One study reported no significant difference in the number of deaths in primary surgery group compared with chemoradiotherapy (15.6% vs 25%, p=0.1),[9] however this study did report a statistically significant 5-year overall survival advantage for those treated with primary surgery (p=0.048).

Stratified results by stage

Some papers provided additional survival information with stratified results or multivariate analyses by stage of cervical cancer.

Yin et al (2011)[14] report that on multivariate analysis survival was superior in stage IB2 cervical cancer patients compared with IIA (p=0.02) but that survival was not significantly different between IB2 and IIB patients (p=0.1). However a multivariate analysis by Kim et al (2009)[17] reported that although patients with stage IB1 had improved PFS compared with stage IIA patients (p=0.02), stage IB2 and stage IIA were not significantly different (p=0.1).

Yamashita et al (2005)[20] reported that the differences in cause-specific survival (CSS) rates between the two treatments of the stage I or stage II patients were not statistically significant (p=0.8407 and p=0.6418).

Dickson et al (2012)[8] reported that women with IB/II cervix cancer were significantly more likely to experience progression, recurrence or death when treated with radiotherapy alone compared with those who had extra peritoneal lymph node dissection OR=10.34; 95% CI: 2.51, 42.65; p=0.0012. Conversely, women with higher stage (III/IV) disease were less likely to experience progression, recurrence, or death when treated with intensity modulated radiotherapy (IMRT) compared with those receiving surgery and radiotherapy, however this was not statistically significant (OR=0.24; 95% CI: 0.05, 1.15; p=0.0746).

Primary surgery followed by adjuvant radiotherapy or chemoradiotherapy

Many women in the primary surgery arms also received adjuvant radiotherapy/ chemoradiotherapy. Two studies provided additional information regarding survival differences between those who had surgery alone and those who had surgery and adjuvant radiotherapy.[9, 11] Both studies reported that patients who had surgery alone had superior survival that those with surgery and adjuvant radiotherapy/chemoradiotherapy. Furthermore, Rungruang et al (2012)[11] reported that any combination with surgery had superior survival than treatment with radiation alone: surgery alone had best overall survival (73 months), followed by patients with surgery and adjuvant radiotherapy (69 months), then patients with radiotherapy and adjuvant surgery (64 months), and lastly radiation alone (54 months) ($p<0.0001$).

Recurrence

Eight studies reported on recurrences/relapses, see Table 3. Recurrence rates ranged from 16.7% to 43% in the primary surgery groups and from 24% to 60.6% in the radiotherapy groups. Two studies reported statistically significant differences between the groups,[13] however in one of these studies there was only a difference reported for distant recurrence.[17] Another small study reported that while overall numbers of recurrences were similar between groups, the percentage of synchronous local and distant metastases was 20% in the primary radiotherapy/chemoradiotherapy group compared with 7% in the primary surgery group (statistical significance not reported).[18] The remaining studies either did not report statistical significance[14, 15] or no significant difference was found.[7, 9, 21]

Table 3 Survival and recurrence reported in studies comparing primary surgery with primary radiotherapy/chemoradiotherapy for cervical cancer

Study	Population	Group	Overall survival		Deaths		PFS/DFS		Recurrences	
				p-value		p-value		p-value		p-value
Baalbergen 2013[135] Systematic review Includes 1 RCT (subset of Maneo 2011[7]) Median follow-up 87mths	Cervical adenocarcinoma (stage IA-IIB) N=46 IB2: not stated	Primary surgery	70%	OR 0.67 (95% CI 0.2 to 2.26) p=0.05			DFS: 66%	OR 0.43 (95% CI 0.13 to 1.43) p=0.02		
		Primary RT or CRT	59%				DFS: 47%			
Maneo 2011[7] RCT, abstract 20yr update	Stage IB-IIA cervical cancer N=327 IB2: not stated	Radical surgery (n=169)	20yr: 72%	p=0.28					48 (28%) (28 in pelvis)	NR
		External RT plus BRT (n=158)	20yr: 77%						46 (28%) (34 in pelvis)	
Rungruang 2012[11] Retrospective cohort M/C Median follow-up not stated	Stage IB2 cervical cancer N=770 IB2: 100%	Primary surgery (n=401) +/- adj RT	72 mths	p<0.0001			DFS 75.0 mths	p=0.001		
		Primary RT (n=369) +/- adj surgery	61.4 mths				DFS 67.5 mths			
Park 2012[9] Retrospective cohort M/C Median follow-up 40mths	IB2 and IIA2 cervical cancer N=215 IB2: 75-78%	RH + adj therapy (n=147)	5yr 78%	p=0.048	23 (15.6%)	p=0.101	RFS 5yr 77%	p=0.047	27 (18.4%)	p=0.068
		Primary CRT (n=68)	5yr 67%		17 (25%)		RFS 5yr 66%		20 (29.4%)	
Yin 2011[14] Retrospective cohort S/C Median follow-up 82.8mths	Locally advanced cervical cancer (stage IB2-IIB) N=476 IB2: 22%	Radical surgery (hysterectomy + pelvic LND) (n=195)	5yr 80.2%	p<0.001	47 (24.1%)	NR	DFS 5yr 77.4%	p<0.001	69 (35.4%)	NR
		CRT (n=94)	5yr 64.4%		36 (38.3%)		DFS 5yr 52.9%		57 (60.6%)	

Study	Population	Group	Overall survival		Deaths		PFS/DFS		Recurrences	
				p-value		p-value		p-value		p-value
Chen 2011[13] Retrospective cohort M/C Median follow-up 77mths	Stage IB1-IIA cervical adenocarcinoma N=258 Majority stage I; IB2: not stated	i) Radical surgery (n=174)	i) mean OS 175.9 mths;	i) vs ii) + iii) p<0.001	i) 27 (16%)	i) vs ii) + iii) <0.001	i) DFI: 170.2 mths	i) vs ii) + iii) p<0.001	i) 32 (18%)	p=0.009
		ii) Radical surgery + adj RT or CRT (n=46)	ii) 130.2 mths		ii) 20 (43.5%)		ii) DFI: 126.3 mths		ii) 20 (43%)	
		iii) RT or CRT (n=38)	iii) mean OS 110.5 mths		iii) 12 (32%)		iii) DFI: 108.1 mths		iii) 13 (34%)	
Turan 2010[15] Retrospective cohort Median follow-up 48.5mths	Stage IB2 cervical cancer N=86 IB2: 100%	RH (n=18)	83%	p=0.20	3 (17%)	NR	77.8%	p=307	4 (22%)	NR
		RT (n=20)	65%		7 (35%)		65%		7 (35%)	
Kim 2009[17] Retrospective cohort S/C Median follow-up 32mths	Stage IB1-iia cervical SCC N=54 IB2: 25%	RH + adj CRT (n=48)	90 mths	p=0.147			PFS 80 mths	p=0.008	8 (16.7%)	Only SS for distant recurrence
		Primary CRT (n=16)	69 mths				PFS 34 mths		7 (43.85%)	
Bansal 2009[16] Retrospective cohort, abstract Median follow-up not stated	Early stage cervical cancer (IB-IIA) N=4885 IB2: not stated	RH (n=4012)		Tumours 4-6cm HR=0.51, 95% CI: 0.36, 0.72; Tumours >6cm NS						
		Primary RT (n=873)								
Zivanovic 2008[18] Retrospective cohort S/C Median follow-up 3.6yrs	Stage IB2 cervical cancer N=47 IB2: 100%	RH (n=27)	3yr 72%	p=0.161			PFS 3yr 52%	p=0.977	10 (37%)	
		Primary RT or CRT (n=20)	3yr 55%				PFS 3yr 55%		8 (40%)	

Study	Population	Group	Overall survival		Deaths		PFS/DFS		Recurrences	
				p-value		p-value		p-value		p-value
Ryu 2007[19] Retrospective cohort M/C Median follow-up 10yrs	Stage IB2 cervical cancer N=692 IB2: 100%	Primary surgery (RH) (alone (n=103) or with adj RT or CRT (n=201));	5yr 89%	RH +/- adj RT/CRT p=NS; CRT +/- adj surg p=NS; RT +/- adj surg p=0.05						
		Primary RT (n=48) or CRT (n=51) Completion surgery (after CRT (n=1) or after RT (n=6))	5yr 84% CRT +/- adj surg; 5yr 73% RT +/- adj surg							
Yamashita 2005[20] Retrospective cohort S/C Median follow-up 43.5mths	Stage I-II cervical carcinoma N=152 ~30% stage IB; IB2: not stated	Surgery (n=115)	5yr CSS 79.9%	p=0.8524	14 (12%)	NR				
		RT (n=37)	5yr CSS 82.3%		8 (32%)					
Macleod 2003[21] Retrospective cohort S/C Median follow-up 6.1yrs	Early stage cervical cancer (IB and IIA) N=127 IB2: not stated	Surgery + adj RT (n=81)	5yr: 86%	p=0.006			5yr RFS: 79%	NS	20 relapses (25%)	NS
		Definitive RT (n=46)	5yr: 58%				5yr RFS: 72%		11 relapses (24%)	

BRT=brachyradiotherapy; CI=confidence interval; CRT=chemoradiotherapy; CSS=cause-specific survival; DFI=disease-free interval; DFS=disease-free survival; HR=hazard ratio; LND=lymph node dissection; M/C=multicentre; NR=not reported; NS=not significant; OR=odds ratio; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; RFS=relapse-free survival; RH=radical hysterectomy; RT=radiotherapy; S/C=single centre; SCC=squamous cell carcinoma; SS=statistically significant

Adverse events/toxicity/surgical morbidity

Nine studies reported on adverse events of surgery and/or radiotherapy/ chemoradiotherapy.[9, 14, 15, 17, 18, 20-22, 135] Adverse events for most of these studies are reported in Table 4. No treatment-related deaths were reported in any of the studies except for the study by Zivanovic et al (2008) where two deaths were reported during primary treatment, both in the primary radiotherapy/chemoradiotherapy group.[18]

Two studies reported higher percentages of late toxicity in patients who received surgery with or without radiotherapy compared to radiotherapy alone (statistical significance not reported).[20, 21] One study[9] showed significantly more grade 3-4 early complications in groups including radiotherapy compared with surgery alone. Two studies reported higher percentages of late toxicity in the radiotherapy alone arm, however overall rates were low in one study,[9] and only significant for grade 4 complications in the other study.[17] One study showed similar rates of adverse events overall between groups, however genitourinary symptoms were observed more frequently in surgery groups, with gastrointestinal symptoms more common in radiotherapy/chemoradiotherapy alone groups.[18] This study also showed more morbidity when surgery was combined with adjuvant therapy compared with surgery alone.[18]

Adverse events included in grade 3-4 complications often included, but were not limited to, bowel obstruction, bowel perforation, fistula formation and proctitis.

Table 4 Adverse events reported in primary surgery studies

Study	Adverse event	Surgery	Surgery + adjuvant therapy	RT/CRT	p-value
Baalbergen 2013[135]	Severe (grade 2 or 3) morbidity	28%		12%	OR 3.32; 95% CI 0.61, 18.12; p=NS
	Short-term morbidity	16%	20%	7%	NR
	Long-term morbidity	24%	29%	16%	NR
Park 2012[9]	Grade 3-4 early complications	2.1%	24.2%	30.9%	p=0.001
	Grade 3-4 late complications	2.1%	1%	8.8%	p=0.026
	Lymphoedema of the lower extremities	12.5%	9.1%	1.5%	p=0.058
Kim 2009[17]	Grade 3-4 late complications of small/large intestine and bladder	25%		31.3%	p=0.745
	Grade 4 late complications	0%		17.8%	p=0.013

Study	Adverse event	Surgery	Surgery + adjuvant therapy	RT/CRT	p-value
Zivanovic 2008[18]	Mild and moderate (grade 1-2) adverse events	81%		85%	NR
	Genitourinary symptoms	30%		15%	NR
	Gastrointestinal symptoms	33%		60%	NR
	Severe (grade 3-4) adverse events	19%	24%	15%	NR
	Severe (grade 3) morbidity	10%	24%		NR
Yamashita 2005[20]	Grade 3+ late toxicity	24%		14%	NR
MacLeod 2003[21]	Grade 3-4 late toxicity		14%	4%	NR

CI=confidence interval; CRT=chemoradiotherapy; NR=not reported; NS=not significant; OR=odds ratio; RT=radiotherapy

Yin et al (2011)[14] reported that the most common adverse effect of surgery was the occurrence of lymphatic retention cysts (12%) and the most common chemotherapy toxicity was alopecia (34%) and leukopenia (grades 3-4) (10%). Other chemotherapy toxicities reported in this study occurred in less than 3% of patients.

One small retrospective cohort reported exclusively on abnormal urodynamic findings following hysterectomy (with or without radiotherapy) or radiotherapy alone.[22] Lin et al (1998)[22] reported that all treatment groups had abnormal voiding function. There were no significant differences between groups for abnormal bladder storing function. Abnormal bladder compliance was seen most often in patients who had both surgery and radiotherapy, significantly more than those who had surgery alone. The radiotherapy and surgery plus radiotherapy groups had the smallest bladder capacity. Groups treated with surgery had high levels of genuine stress incontinence.

Quality of life

Data on quality of life were not reported in any of the primary surgery studies. Although the systematic review included QoL as an outcome, the included RCT did not report on this.

Fertility outcomes

No fertility outcomes were reported in any of the primary surgery studies.

3.1.1 Summary

Fourteen studies, including one randomised controlled trial (RCT), were identified which investigated the use of primary surgery compared with primary radiotherapy/ chemoradiotherapy. The literature indicated that survival may be improved in patients treated with primary surgery compared with primary radiotherapy/chemoradiotherapy, however results were inconsistent. Recurrences appear to be more common in patients treated with radiotherapy, however differences were often not statistically significant. Adverse events were often not statistically significantly different between groups. No quality of life or fertility outcomes were reported.

3.2.2 Trachelectomy

Three citations were identified which compared trachelectomy with hysterectomy for early cervical cancer (including stage IB2). Two studies were reported in abstracts only, therefore information available was limited. It was noted that a number of other studies comparing trachelectomy with hysterectomy were identified in the search, however most of these studies excluded tumours larger than 2cm in diameter (therefore stage IB2 was not included).

The citations included:

- One case-control study, reported in an abstract only,[23] which compared survival outcomes between nerve-sparing radical abdominal trachelectomy and nerve sparing radical hysterectomy.
- Two surveys[24, 25] comparing adverse event/quality of life concerns such as sexual function between radical trachelectomy and radical hysterectomy for early-stage cervical cancer.

Quality assessment

As two citations were reported in abstract only, not enough detail was provided to assess quality. The full text paper was considered of low/medium quality because minimisation of selection bias was unclear and baseline characteristics were not all balanced between groups.

Study characteristics

Characteristics of studies investigating trachelectomy compared with hysterectomy are provided in Table 5. While stage IB2 appeared to be included within the study populations, the percentage of stage IB2 patients was not stated in any of the three studies.

Patient selection criteria

The study by Carter et al (2010) reported in the full text paper[24] was the only one with enough detail to assess patient selection criteria. Patients self-selected whether to undergo trachelectomy or hysterectomy. Women aged between 18 and 45 were included in this study, however women in the trachelectomy group were younger than those in the hysterectomy group (mean 32.6 years versus 37.6 years, respectively). Clinical/tumour characteristics of the patients were not provided, however the study included stage IA1 with lymphovascular space involvement, and IA2-IB2 cervical cancer. The majority of women choosing trachelectomy indicated fertility and not having enough time to complete childbearing as factors in the treatment decision-making process. These women also reported preoperative desires for ovarian preservation for future fertility options or menopause prevention.

Table 5 Characteristics of studies comparing trachelectomy with hysterectomy for stage IB2 cervical cancer

Study	Population	Intervention	Control	Outcomes	Quality
Van Gent 2011[23] Case-control study, abstract	Early stage cervical cancer (stage IA2-IIA) N=116 IB2: not stated	Nerve-sparing radical abdominal trachelectomy (n=29)	Nerve-sparing RH (n=87)	OS, DFS, recurrence	Unable to be assessed
Song 2011[25] Cross-sectional study – single survey, abstract	Early stage cervical cancer N=81* IB2: not stated	Radical trachelectomy (n=18)	RH (n=24)	Sexual function	Unable to be assessed
Carter 2010[24] Prospective study - survey	Early-stage cervical cancer (stage IA1 with lymphovascular space involvement, IA2-IB2) Preoperative sample N=71; 2-year assessment N=52 IB2: not stated	Radical trachelectomy (n=43) (76% vaginal, 24% abdominal)	RH (n=28)	Mood, distress, QoL, sexual function	Low/medium

*this study also included 39 patients treated by cervical conization. DFS=disease-free survival; OS=overall survival; QoL=quality of life; RH=radical hysterectomy

Survival

Only one study reported survival outcomes between trachelectomy and hysterectomy.[23] The case-control study by van Gent et al (2011)[23] reported that overall survival was similar between nerve-sparing abdominal radical trachelectomy (5yr OS 96.6%) and nerve-sparing radical hysterectomy (5yr OS 93.1%) (significance not stated). Disease-free survival was not significantly different between the groups (5yr DFS 93.1% in trachelectomy group; 5yr DFS 86.2% in hysterectomy group).

Recurrence

The van Gent study also reported that there was no significant difference in recurrences between patients treated with nerve-sparing abdominal radical trachelectomy and those treated with nerve-sparing radical hysterectomy (6.9% versus 11.5% respectively).[23]

The paper by Carter et al (2010)[24] noted that two women withdrew over the course of the study due to recurrence, one in each group.

Adverse events/toxicity/surgical morbidity

The two qualitative studies reported that both trachelectomy and hysterectomy groups experienced sexual dysfunction; however there were no significant differences between the groups.[24, 25]

No other adverse events were reported in any of the trachelectomy studies.

Quality of life

Other than sexual dysfunction, quality of life outcomes were only reported in the prospective survey by Carter et al (2010).[24]

Carter et al (2010)[24] reported data on mood, distress, quality of life, fear of cancer recurrence, and reproductive concerns. The scores on measurements of mood, distress, sexual function, fear of recurrence, and quality of life did not differ significantly between groups. Treatment choice was influenced by the desire to preserve fertility. Quality of life scores improved in both groups over time.

Obstetric outcomes

Although the study by Carter et al (2010),[24] reported that the desire to preserve fertility influenced treatment choice, no obstetric outcomes (such as rates of successful pregnancy following trachelectomy) were reported.

Further information regarding successful pregnancy following trachelectomy reported in non-comparative studies is presented in Section 3.4.

3.2.2 Summary

Only three comparative studies investigating trachelectomy in populations including stage IB2 cervical cancer were identified (most studies on trachelectomy exclude tumours >2cm diameter). Of these studies, two were reported as abstracts only. No differences were reported between trachelectomy and hysterectomy for survival, recurrence, sexual dysfunction or quality of life. No fertility outcomes were reported in the comparative studies.

3.2.3 Completion surgery

Eight citations describing seven studies were identified comparing the addition of hysterectomy after primary radiotherapy/chemoradiotherapy compared with radiotherapy/chemoradiotherapy alone.

The citations included:

- Three RCTs[26-29] investigating hysterectomy following radiotherapy/ chemoradiotherapy compared with radiotherapy/chemoradiotherapy alone.
- Four retrospective studies[30-33] investigating hysterectomy following chemoradiotherapy compared with chemoradiotherapy alone.

Quality assessment

The RCTs included in this section were considered to be of medium/high quality. The retrospective studies were considered low/medium to medium quality, mainly due to a lack of information regarding how patients were selected for each treatment.

Study characteristics

Study characteristics for papers investigating completion surgery are described in Table 6. Two studies (including one RCT) included only stage IB2 patients,[29, 33] one study included >50%,[28] and four studies included <25% stage IB2 patients.[26, 30-32]

Patient selection criteria

The RCTs included a large age range (18-70 years). Patients were required to have adequate organ function and good performance status. Patients with metastasis to the para-aortic lymph nodes were explicitly excluded in the three RCTs.[26, 28, 29] Due to the retrospective nature of the remaining studies, detailed information on patient selection criteria was not available.

Table 6 Characteristics of comparative studies investigating completion surgery for stage IB2 cervical cancer

Study	Population	Intervention	Control	Outcomes	Quality
Cetina 2013[26] RCT	IB2-IIB cervical cancer N=211 IB2: 16-18%	External beam chemoradiation followed by radical hysterectomy (n=111)	External beam chemoradiation followed by brachytherapy (n=100)	OS, PFS, toxicity, complications	Medium/high
Cetina 2010*[27] RCT, abstract	IB2-IIB cervical cancer N=220 IB2: not stated	External beam chemoradiation followed by radical hysterectomy (n=113)	External beam chemoradiation followed by brachytherapy (n=107)	OS, PFS, toxicity	
Morice 2012[28] RCT - GYNECO 02	Stage IB2 or II cervical cancer N=61 IB2: 50-52%	Chemoradiation followed by hysterectomy (n=31)	Chemoradiation alone (n=30)	OS, EFS	Medium/high
Keys 2003[29] RCT	Bulky stage IB cervical cancer (≥4cm) N=256 IB2: 100%	Attenuated irradiation followed by extrafascial hysterectomy (n=132)	External and intracavitary irradiation (n=124)	OS, PFS, adverse events	Medium/high
Chereau 2013[32] Retrospective cohort S/C	Locally advanced cervical cancer (IB2-IIB) N=80 IB2: 24%	Completion surgery after chemoradiotherapy (n=46)	Chemoradiotherapy (n=34)	OS, DFS	Low/medium
Leguevaque 2011[31] Retrospective M/C	Locally advanced cervical cancer (stages IB2, IIA >4cm, IIB, IIIA, IIIB, IVA; IB1 if had lymph node invasion) N=111 IB2: 20%	Completion surgery after chemoradiotherapy (n=67)	Chemoradiotherapy (n=44)	OS, PFS	Low/medium

Study	Population	Intervention	Control	Outcomes	Quality
Cetina 2009[30] Retrospective case-control S/C	IB2-IIB cervical cancer N=80 IB2: 22%	External beam chemoradiation followed by radical hysterectomy (n=40)	External beam chemoradiation followed by brachytherapy (n=40)	OS, PFS, toxicity	Medium
Darus 2008[33] Retrospective cohort S/C?	IB2 cervical cancer N=54 IB2: 100%	Extra-fascial hysterectomy following chemoradiotherapy (n=24)	Chemoradiotherapy (n=30)	OS, DFI, toxicity	Medium

*Although patient number slightly differ between this abstract and the Cetina 2013 full text paper, outcome data from the full text paper has been used as more detail is available.
DFI=disease-free interval; DFS=disease-free survival; EFS=event-free survival; M/C=multicentre; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; S/C=single centre

Survival

Survival outcomes for the completion surgery studies are presented in Table 7.

Overall survival

All of the six studies that reported overall survival found no significant difference between patients treated with surgery after radiotherapy/chemoradiotherapy and those treated with radiotherapy/chemoradiotherapy alone.[26, 28-30, 32, 33]

Progression-free/disease-free survival

The same six studies reported no significant difference for progression-free or disease-free survival between patients treated with surgery after radiotherapy/chemoradiotherapy and those treated with radiotherapy/chemoradiotherapy alone.[26, 28-30, 32, 33]

One multicentre retrospective cohort reported that completion surgery improved disease-free survival compared with chemoradiotherapy alone.[31]

Recurrence

Five studies reported on recurrence, see Table 7.

No difference between groups was observed in two studies (one RCT, one retrospective case-control study).[26, 30] One small RCT reported a higher percentage of recurrence in the completion surgery group (26% vs 13%, statistical significance not reported).[28] However, one retrospective study reported higher rates of recurrence in the chemoradiotherapy alone group (36.4% vs 22.4%, p=0.01).[31] Another retrospective study reported slightly higher recurrence rates in the chemoradiotherapy alone group (17% vs 13%), however statistical significance was not reported.[33]

Table 7 Survival and recurrence reported in comparative studies investigating completion surgery for cervical cancer

Study	Population	Groups	Overall survival		DFS/PFS		Deaths		Recurrence	
				p-value		p-value		p-value		p-value
Cetina 2013[26] RCT Median follow-up 36mths	IB2-IIB cervical cancer N=211 IB2: 16-18%	External beam CRT followed by RH (n=111)	74.50%	HR 0.698 (95% CI 0.31, 1.34) p=0.236	PFS 71.70%	HR 0.65 (95% CI 0.35, 1.21) p=0.186			13 (11.7%) (7 local, 6 systemic)	p=0.918
		External beam CRT followed by BT (n=100)	76.30%		PFS 74.80%				15 (15%) (10 local, 5 systemic)	
Morice 2012[28] RCT Median follow-up 3.8yrs	Stage IB2 or II cervical cancer N=61 IB2: 50-52%	CRT followed by hysterectomy (n=31)	3yr 86%	p=0.15	3yr EFS 72%	p=0.17			8 (26%)	
		CRT alone (n=30)	3yr 97%		3yr EFS 89%				4 (13%)	
Keys 2003[29] RCT Median follow-up 9.6yrs	Bulky stage IB cervical cancer (≥4cm) N=256 IB2: 100%	Attenuated RT followed by extrafascial hysterectomy (n=132)		RR 0.89 (90% CI: 0.65, 1.21) p=0.26 (one tail)	PFS median not reached (53% at 8.4 yrs)	RR 0.77 p=0.07 (one tail)	55 (42%) (44 disease related, 1 treatment related)			
		External and intracavitary RT (n=124)			PFS median 7.4 yrs		55 (44%) (43 disease related, 2 treatment related)			
Chereau 2013[32] Retrospective cohort S/C	Locally advanced cervical cancer (IB2-IIB)	Completion surgery after CRT (n=46)		p=0.92		DFS p=0.75				
		CRT (n=34)								

Study	Population	Groups	Overall survival		DFS/PFS		Deaths		Recurrence	
				p-value		p-value		p-value		p-value
Median follow-up 30.7mths	N=80 IB2: 24%									
Leguevaque 2011[31] Retrospective cohort M/C Median follow-up not stated	Locally advanced cervical cancer (stages IB2, IIA >4cm, IIB, IIIA, IIIB, IVA; IB1 if had lymph node invasion) N=111 IB2: 20%	Completion surgery after CRT (n=67)			DFS 4yr 66%	p=0.01	11 (16.4%)	NR	15 (22.4%); median time to recurrence 14 mths	p=0.01; NR
		CRT (n=44)			DFS 4yr 49.7%		9 (20.4%)		16 (36.4%); median time to recurrence 11 mths	
Cetina 2009[30] Retrospective case-control S/C Median follow-up 22-26mths	IB2-IIB cervical cancer N=80 IB2: 22%	External beam CRT followed by RH (n=40)	5yr 78% (projected)	NS		NS	8		8	
		External beam CRT followed by BT (n=40)	5yr 78% (projected)				8		8	
Darus 2008[33] Retrospective cohort S/C? Median follow-up 46.8mths	IB2 cervical cancer N=54 IB2: 100%	Extra fascial hysterectomy following CRT (n=24)	Mean 113.8 mths	p=0.82	DFS mean 113.8 mths	p=0.75	4 (17%)		3 (13%)	
		CRT (n=30)	Mean 113.7 mths		DFS mean 113.2 mths		4 (13%)		5 (17%)	

BT=brachytherapy; CI=confidence interval; CRT=chemoradiotherapy; DFS=disease-free survival; EFS=event-free survival; HR=hazard ratio; M/C=multicentre; NR=not reported; NS=not significant; PFS=progression-free survival; RCT=randomised controlled trial; RH=radical hysterectomy; RR=relative risk; S/C=single centre

Adverse events/toxicity/surgical morbidity

Adverse events for completion surgery were reported in five studies.[26, 29, 30, 32, 33]

The RCT by Cetina et al (2013) reported that while there appeared to be more reports of proctitis, cystitis and hydronephrosis in the chemoradiotherapy alone group, this was not statistically significantly different compared with the surgery group.[26]

The RCT by Keys et al (2003) reported that while hysterectomy did not increase the frequency of reported grade 3-4 adverse events (10% in each treatment group), the frequency of any reported adverse event was higher for those treated with hysterectomy compared with radiotherapy alone (63% vs 56%, respectively; statistical significance not reported).[29] This trial reported that there was one treatment-related death in the surgery group and two in the radiotherapy group.[29]

Darus et al (2008) also reported that the addition of hysterectomy did not increase rates of adverse events, with two grade 3-4 complications in each group.[33] Gastrointestinal toxicity appeared higher in the chemoradiotherapy group but this was not statistically significant (41% vs 21%, p=0.1). No treatment related deaths occurred in this study.

Surgical morbidities such as wound infection and gastrointestinal or genitourinary fistulas were sometimes reported, however rates were low.[26, 30, 32]

Quality of life

Data on quality of life were not reported in any of the completion surgery studies.

Fertility outcomes

No fertility outcomes were reported in any of the completion surgery studies.

3.2.3 Summary

Seven studies, including three RCTs, were identified which investigated the addition of hysterectomy following primary radiotherapy/chemoradiotherapy (completion surgery). Completion surgery does not appear to have any survival benefit compared with radiotherapy/chemoradiotherapy alone. Completion surgery may reduce the risk of recurrence (particularly distant metastases), however results were inconsistent between studies. No major differences in adverse events between groups were reported. Quality of life and fertility outcomes were not reported in any of the completion surgery studies.

3.2.4 Different surgical methods for performing hysterectomy

In addition to the previous papers investigating the effectiveness of surgery in the management of cervical cancer, a number of studies were identified which compared different surgical methods for performing hysterectomy. Papers investigating detailed levels of surgery such as incision methods or level of resection were not included.

The following citations were identified:

- One **systematic review** on laparoscopic, robotic and open method of radical hysterectomy for cervical cancer.[34] This review includes some, but not all, of the papers below along with other papers as this review is not specific to stage.
- The following surgical methods have been investigated:
    - Laparoscopic versus open/abdominal radical hysterectomy (laparotomy): 14 retrospective studies[35-48], and one prospective study (abstract only).[136]
    - Laparoscopic versus laparotomic extraperitoneal versus laparotomic transperitoneal pelvic lymphadenectomy: one **RCT.**[49]
    - Laparoscopically assisted radical vaginal hysterectomy versus abdominal radical hysterectomy: one **systematic review** (abstract only),[50] one prospective study[51] and two retrospective studies.[52, 53]
    - Simple versus radical hysterectomy: one retrospective study.[54, 55]
    - Class II versus class III radical hysterectomy: one **RCT.**[56]
    - Total extraperitoneal radical hysterectomy with intraperitoneal abdominal radical hysterectomy: one prospective trial (abstract only).[57]
    - Class I versus class II versus class III vaginal hysterectomy: one retrospective study.[58]
    - Nerve-sparing radical hysterectomy versus conventional radical hysterectomy: one **RCT**,[59] one prospective study[60] and one retrospective study[61] – all abstracts.
    - Robot assisted surgery:
        - Three **systematic reviews** on robot-assisted surgery, of which two are on gynaecologic cancer,[62, 63] one specifically on early stage cervical cancer.[64]
        - Three prospective[65-67] and three retrospective[68-70] studies comparing robotic assisted surgery with open/abdominal radical hysterectomy. One of the prospective studies[67] and one additional retrospective study compared robotic assisted surgery with laparoscopic radical hysterectomy.[71]

Outcome data are presented from the systematic reviews and RCTs only. Note that the systematic reviews did not include any RCTs, therefore they are considered level III evidence. Outcome data from the primary non-randomised trials have not been included as the main comparisons of open/abdominal, laparoscopic and robotic hysterectomy are summarised in the systematic reviews. However, it is noted that the systematic reviews do not include all of the other identified references.

Quality assessment

Two systematic reviews were considered to be of high quality, one medium quality and two low/medium quality. The lower quality reviews did not perform quality assessment or explore heterogeneity between studies. The RCTs were considered to be of high quality, except for one study which reported in an abstract only therefore not enough detail was available to assess quality.

Study characteristics

Characteristics for papers comparing different surgical methods for performing hysterectomy are described in Table 8. Four of the five systematic reviews compared robotic-assisted radical hysterectomy with open/abdominal and/or laparoscopic radical hysterectomy.[34, 62-64] The other systematic review compared laparoscopic-assisted radical vaginal hysterectomy (LARVH) with abdominal radical hysterectomy.[50] Each RCT identified compared different surgical methods to perform hysterectomy. The percentage of stage IB2 patients included was not stated in any of the systematic reviews or RCTs.

Table 8 Characteristics of papers comparing different surgical methods for performing hysterectomy for cervical cancer

Study	Population	Intervention	Control	Outcomes	Quality
Geetha 2012[34] Systematic review	Cervical cancer (stage not defined) N=1339 laparoscopic RH; 1552 open RH; 327 robotic RH IB2: not stated	Laparoscopic and robotic RH	Abdominal RH	Surgical outcomes	Medium
Kucukmetin 2011[50] Systematic review, abstract – includes 1 RCT	Early cervical cancer N=13 IB2: not stated	Laparoscopic assisted radical vaginal hysterectomy (LARVH)	Radical abdominal hysterectomy	Surgical outcomes	High
Shi 2012[62] Systematic review	Gynaecological cancer N=21 CCTs IB2: not stated	Robotic surgery	Non-robotic surgery or different types of robotic assistants	OS, DFS, surgical outcomes, QoL	High
Kruijedberg 2011[64] Systematic review	Early cervical cancer N=27 studies including 1256 patients 8.2-14% >1B1; IB2: not stated	Robot-assisted RH	Total laparoscopic RH	Surgical outcomes	Low/ medium
Leguevaque 2011b[63] Systematic review	Early cervical cancer N=10 studies IB2: not stated	Robotic surgery	Open or laparoscopic surgery	Surgical outcomes	Low/ medium
Lu 2009[59] RCT, abstract	Stage IB1-IIA cervical cancer N=31 IB2: not stated	Nerve-sparing RH	Classical RH	Urodynamic findings, QoL	unable to be assessed

Study	Population	Intervention	Control	Outcomes	Quality
Benedetti Panici 2006[49] RCT	Stage IB-IIB cervical cancer N=168 57% stage IB2-IIB, IB2: not stated	Transperitoneal and extraperitoneal pelvic lymphadenectomy	Laparoscopic pelvic lymphadenectomy	Feasibility, surgical outcomes, complications	High
Landoni 2001[56] RCT	Stage IB-IIA cervical cancer N=243 91-93% IB; 24-25% >4cm; IB2: not stated	Class II RH (removal of the median half of the cardinal and uterosacral ligaments, ligating the uterine artery at the ureter)	Class III RH (removal of the central lesion with wide radical excision of the parametrial and paravaginal tissue. The uterine artery is ligated at its origin; the lateral and posterior parametria are resected to the pelvic side walls and several centimetres of vagina are removed)	OS, DFS, recurrence, morbidity	High

CCT=controlled clinical trial; DFS=disease-free survival; LARVH=Laparoscopic assisted radical vaginal hysterectomy; OS=overall survival; QoL=quality of life; RCT=randomised controlled trial; RH=radical hysterectomy

Outcomes

Most studies identified in this section focused on differences in surgical outcomes, such as estimated blood loss and operation times, for the different surgical methods explored.

Survival

Robotic hysterectomy

Only one of the three systematic reviews on robotic surgery reported survival outcomes. Shi et al (2012)[62] reported no difference in either overall or disease-free survival between robotic surgery, or laparoscopy or laparotomy.

No other papers reported on survival.

Recurrence

Robotic hysterectomy

Only one of the three systematic reviews on robotic surgery reported on recurrence. Kruijedberg et al (2011)[64] reported that recurrence was similar between robot-assisted radical hysterectomy and laparoscopic radical hysterectomy.

No other papers reported on recurrence.

Surgical morbidity

Open/laparoscopic/robotic radical hysterectomy

The mean operation times appear to be similar between robotic and laparoscopic radical hysterectomy[34, 64] and open radical hysterectomy.[34] However the systematic review by Shi et al (2012)[62] did not pool results for total operating time due to high heterogeneity and the review by Leguvaque et al (2011b)[63] reported mixed results comparing robotic and laparoscopic radical hysterectomy (similar in two studies, longer for robotic in three studies, shorter for robotic in one study).

Mean blood loss was reported to be higher for open radical hysterectomy than robotic[34, 63] or laparoscopic[34] radical hysterectomy. Mean blood loss appeared to be similar between laparoscopic and robotic radical hysterectomy.[34, 64]

Hospital stay was reduced for patients receiving robotic radical hysterectomy compared with open radical hysterectomy.[34, 62, 63] The review by Kruijdenberg et al (2011) also reported shorter hospital stay for patients receiving robotic radical hysterectomy compared with laparoscopic radical hysterectomy.[64]

Class II versus class III radical hysterectomy

One RCT reported that mean blood loss, need for blood transfusions and hospital stay were similar between class II and class III radical hysterectomy, however operating time was significantly shorter for class II radical hysterectomy.[56]

Vaginal hysterectomy

A small RCT reported that laparoscopically assisted radical vaginal hysterectomy (LARVH) was associated with less blood loss, shorter hospital stay and less requirement for pain medication than abdominal (open) radical hysterectomy, with no significant difference in operation-related complications.[50]

Pelvic lymphadenectomy

One RCT compared various techniques of pelvic lymphadenectomy.[49] Mean operation time was shortest for extraperitoneal, followed by transperitoneal and then laparoscopic pelvic lymphadenectomy. Mean blood loss and requirement for blood transfusions were similar between groups. Transperitoneal pelvic lymphadenectomy was associated with longer hospital stay and more post-operative pain than the other two techniques.

Adverse events

Open/laparoscopic/robotic radical hysterectomy

The systematic review by Geetha et al (2012)[34] reported that post-operative infectious morbidity was significantly higher for open radical hysterectomy than other methods, however post-operative non-infectious morbidity was similar between methods. The review by Shi et al (2012)[62] reported that there were more post-operative complications with open hysterectomy than robotic hysterectomy, with no difference between robotic and laparoscopic hysterectomy.

Kruijedberg et al (2011)[64] reported that although percentages of major intra-operative complications were comparable between robotic and laparoscopic radical hysterectomy, the type of complications differed. Laparoscopic surgery was associated with more vascular and bladder injury, however, more nerve injury was observed with robotic surgery. Robotic radical hysterectomy was associated with a higher percentage of major post-operative complications compared with laparoscopic surgery (9.6% vs 5.5%, p<0.05).

Leguevaque et al (2011b)[63] reported that intraoperative and post-operative complications were similar between robotic and open radical hysterectomy.

Class II versus class III radical hysterectomy

Similar rates of intraoperative and early complications were observed in the RCT comparing class II and class III radical hysterectomy.[56] Late morbidity was significantly lower in class II hysterectomy (especially urologic morbidity: 13% vs 28%).

Nerve-sparing radical hysterectomy

Compared with radical hysterectomy, nerve-sparing radical hysterectomy had shorter suprapubic drainage and superior recovery for detrusor pressure and bladder compliance.[59]

Vaginal hysterectomy

No significant difference in operation-related complications were reported between laparoscopically-assisted vaginal radical hysterectomy and abdominal radical hysterectomy.[50]

Pelvic lymphadenectomy

No intraoperative bowel or urinary complications were reported in the RCT comparing different methods of pelvic lymphadenectomy. There was no significant difference between transperitoneal, extraperitoneal or laparoscopic pelvic lymphadenectomy for the following post-operative complications: lymphocyst, deep vein thrombosis, lymphoedema, mild paraesthesia, fever or surgical site infection.

Quality of life

Nerve-sparing radical hysterectomy

Compared with radical hysterectomy, nerve-sparing radical hysterectomy had superior quality of life in terms of social and family life, emotional well-being, working status and the symptom correlated with operating field (p<0.05).[59]

No other papers reported on quality of life.

3.2.4 Summary

Thirty-eight papers, including five systematic reviews and three RCTs, were identified comparing different methods for performing radical hysterectomy. The most commonly reported comparisons were between open/abdominal radical hysterectomy, laparoscopic radical hysterectomy and/or robotic radical hysterectomy. Outcome data from the systematic reviews and RCTs were included in this review. Limited information on survival and

recurrence were reported, although there was some indication that there is no difference in these outcomes between robotic and non-robotic methods for performing hysterectomy. Open/abdominal radical hysterectomy appears to have worse surgical outcomes (such as higher estimated blood loss and longer hospital stay) and adverse events than robotic hysterectomy. Most studies reported no significant difference in surgical outcomes between robotic and laparoscopic hysterectomy. One RCT reported that class II hysterectomy had shorter operation time than class III hysterectomy, however no other differences in outcomes were reported. A small RCT reported superior surgical outcomes for laparoscopically assisted radical vaginal hysterectomy compared with open radical hysterectomy.

3.3 Neoadjuvant chemotherapy for treatment of women with stage IB2 cervical cancer

Summary of included papers

Three high quality systematic reviews about the use of neoadjuvant chemotherapy to treat early/locally advanced cervical cancer were identified.[72-74] A fourth review was identified[75] however this was published in 1998 and results have been superseded by those reported in the more recent reviews, therefore results from the 1998 review have not been included.

Two of the systematic reviews included papers comparing neoadjuvant chemotherapy followed by surgery with primary surgery.[72, 73] The third systematic review included a broader range of comparisons including papers comparing neoadjuvant chemotherapy followed by local treatment (not necessarily surgery) with local treatment alone as well as papers comparing neoadjuvant chemotherapy followed by surgery with exclusive radiotherapy. [74]

Eleven randomised controlled trials were identified,[76-86] of which only four had not been included in the systematic reviews. Two of the four RCTs investigated different neoadjuvant chemotherapy regimens.[85, 86] Of the other two, one paper identified contained updated results from a trial which had been included in the reviews,[76] the other paper had been excluded from one of the previous reviews[73] because chemotherapy was allowed on both arms (any patients not amenable to surgery received chemoradiotherapy instead).[77] The remaining seven RCTs that were included in the systematic reviews have not been reported separately in this current review, but included in the pooled results presented in the systematic reviews.

An additional 25 non-randomised comparative studies (23 on neoadjuvant chemotherapy versus local treatment[14, 15, 19, 87-106] and two comparing different regimens[107, 108]) were identified however due to higher levels of evidence being available (systematic reviews – Level I and RCTs – Level II),[137] the results from these studies have not been reported in this review.

Included papers have been divided into the following subgroups:

- **3.3.1 Neoadjuvant chemotherapy versus local treatment:** papers investigating the use of neoadjuvant chemotherapy followed by local treatment (usually surgery) compared with local treatment alone.

- **3.3.2 Different neoadjuvant chemotherapy regimens:** papers comparing different regimens for neoadjuvant chemotherapy.

Quality assessment

The systematic reviews were considered to be of high quality. The RCTs were considered to be of medium quality as although they were randomised appropriately, minimised selection bias, standardised outcome assessment and contained well balanced groups, they were not adequately powered to detect survival differences. One phase II trial was reported in abstract only with not enough detail provided to assess quality.

Study characteristics

The study characteristics of all citations included in this research question are provided in Table 9.

The systematic review by Kim et al (2013)[72] included only early-stage cervical cancer (stage IB1-IIA), however the other two reviews included locally advanced cervical cancer.[73, 74] Kim et al (2013)[72] and Rydzewska et al (2012)[73] included the same RCTs, except the Rydzewska review also included an additional RCT by Chen et al (2008).[80]

The additional RCTs included between 26%[77] and 68%[86] of stage IB2 patients within the treatment groups.

The trials all used cisplatin-based chemotherapy, although treatment regimens varied.[72-74] The RCT by Wen et al (2012)[77] used cisplatin plus 5-fluorouracil, the RCT by Katsumata et al (2013)[76] used a combination of bleomycin, vincristine, mitomycin and cisplatin. The phase II SNAP trials compared the three-drug combination of paclitaxel/ifosfamide/cisplatin (TIP) with two-drug combinations ifosfamide/cisplatin (IP)[85] or paclitaxel/cisplatin (TP).[86]

Patient selection criteria

The additional RCTs included a large age range (from 18-20 years to 70-75 years) and patients were required to have good performance status and adequate organ function to be considered as suitable surgical candidates.[76, 77]

Table 9 Characteristics of neoadjuvant chemotherapy studies

Study	Population	Intervention	Control	Outcomes	Quality
Systematic reviews					
Kim 2013[72] Systematic review and meta-analysis	Stage IB1-IIA cervical cancer 5 RCTs and 4 observational studies included; 1784 pts IB2: 44%	NACT followed by surgery	Primary surgery	OS, PFS, recurrence	High
Rydzewska 2012[73] Systematic review and meta-analysis	Early-stage or locally advanced cervical cancer 6 RCTs including 1078 pts IB2: not stated	NACT followed by radical surgery	Radical surgery	OS, PFS, recurrence, radical resection, surgical morbidity	High (Cochrane review)
Tierney 2004[74] Systematic review and meta-analysis	Locally advanced cervical cancer (IB-IVA) i) 18 RCTs including 2074 pts; ii) 5 RCTs including 872 pts i)12% IB; ii) 35-36% IB/IIA; IB2: not stated	i) NACT followed by local treatment; ii) NACT followed by surgery	i) local treatment alone; ii) radiotherapy	OS, DFS, MFS	High (Cochrane review)
Randomised controlled trials					
Katsumata 2013[76] RCT – JCOG 0102	Stage IB2, IIA2 or IIB squamous cell carcinoma of the uterine cervix N=134 IB2: 36-39%	NACT followed by surgery (n=67)	Radical hysterectomy (n=67)	OS, PFS, response rate, toxicity, morbidity	Medium
Wen 2012[77] RCT	Stage IB2-IIA cervical cancer N=124 IB2: 26.7-38.7%	i) intravenous NACT followed by radical surgery (n=30); ii) intra-arterial NACT followed by radical surgery (n=31)	iii) type III radical surgery (n=31); iv) brachytherapy followed by radical surgery (n=31)	OS, PFS, recurrence, response to neoadj treatment, toxicity	Medium

Study	Population	Intervention	Control	Outcomes	Quality
Comparing different neoadjuvant chemotherapy regimens					
Buda 2005[85] - SNAP 01 RCT – phase II	Locally advanced squamous cell cervical carcinoma (IB2-IVA) N=219 IB2: 46-49%	NACT - paclitaxel/ifosfamide/ cisplatin (TIP) (n=106)	NACT - ifosfamide/cisplatin (IP) (n=113)	OS, PFS, toxicity, response to chemotherapy	Medium
Fossati 2005[86] - SNAP 02 RCT – phase II, abstract	Locally advanced squamous cell cervical carcinoma N=156 IB2: 58-62%	NACT - paclitaxel/ifosfamide/ cisplatin (TIP) (n=76)	NACT - paclitaxel/cisplatin (TP) (n=80)	Pathological response, toxicity	Unable to be assessed

DFS=disease-free survival; IP=ifosfamide/cisplatin; JCOG=Japan Clinical Oncology Group; MFS=metastases-free survival; NACT=neoadjuvant chemotherapy; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; SNAP=Studio Neo-Adjuvante Portio; TIP=paclitaxel/ifosfamide/cisplatin; TP=paclitaxel/cisplatin

Outcomes

3.3.1 Neoadjuvant chemotherapy versus local treatment

Survival

The three reviews reported pooled results for overall survival and disease-free survival, see Table 10. The two most recent systematic reviews reported contradictory results regarding the effect on survival of neoadjuvant chemotherapy followed by surgery compared with surgery alone.

Kim et al (2013)[72] reported that there was no difference in overall survival seen between treatment groups for RCTs and observational studies combined (HR 1.12; 95% CI 0.88, 1.36; p=0.32) or for RCTs (HR 0.95; 95% CI 0.74, 1.22; p=0.71). However when observational studies were analysed separately, neoadjuvant chemotherapy (NACT) was associated with worse OS (HR 1.68; 95% CI 1.12, 2.53; p=0.01) than primary surgery.

However, Rydzewska et al (2012)[73] reported that survival was improved in the NACT group using both fixed effect (HR 0.77; 95% CI 0.62, 0.96; p=0.02) or random effects models (HR 0.76; 95% CI 0.59, 0.99; p=0.04), compared with primary surgery.

The review by Tierney et al (2004)[74] reported significant heterogeneity between trials comparing neoadjuvant chemotherapy followed by local treatment to local treatment therefore trials were grouped by chemotherapy cycle length or planned cisplatin dose intensity. The review reported that neoadjuvant chemotherapy tended to improve survival in trials using chemotherapy cycle lengths shorter than 14 days or cisplatin dose intensities greater than 25 mg/m^2 per week. In contrast, neoadjuvant chemotherapy led to worse survival in trials using cycle lengths longer than 14 days or cisplatin dose intensities less than 25 mg/m^2 per week. Neoadjuvant chemotherapy followed by surgery appeared to improve survival compared with exclusive radiotherapy (HR=0.65, 95% CI=0.53 to 0.80, p=0.0004), however heterogeneity was noted in both the design and results of the trials.

In the additional RCT[77] and updated results from the JCOG 0102 trial[76] not included in the reviews, there was no significant difference in overall or disease-free/progression free survival between neoadjuvant chemotherapy and primary surgery groups, see Table 11.[76, 77]

The JCOG 0102 trial noted that, within the treatment groups, survival was superior for patients with stage IB2 cervical cancer compared to stage IIA2/IIB; however statistical significance was not reported.[76]

Table 10 Survival outcomes reported in neoadjuvant chemotherapy systematic reviews

Review	Included trials	Comparison	Overall survival	Progression-free survival
Kim 2013[72]	5 RCTs, 4 observational studies	NACT followed by surgery vs primary surgery	All: HR 1.12; 95% CI 0.88, 1.36; p=0.32 RCTs: HR 0.95; 95% CI 0.74, 1.22; p=0.71 Observational studies: HR 1.68; 95% CI 1.12, 2.53; p=0.01	All: HR 1.12; 95% CI 0.85, 1.46; p=0.42 RCTs: HR 1.01; 95% CI 0.74, 1.39; p=0.94 Observational studies: HR 1.43; 95% CI 0.87, 2.37; p=0.16
Rydzewska 2012[73]	6 RCTs	NACT followed by surgery vs primary surgery	Fixed: HR 0.77; 95% CI 0.62, 0.96; p=0.02 Random: HR 0.76; 95% CI 0.59, 0.99; p=0.04	Fixed: HR 0.75; 95% CI 0.61, 0.93; p=0.008 Random: HR 0.72; 95% CI 0.55, 0.95; p=0.02
Tierney 2004[74]	18 RCTs	NACT followed by local treatment vs local treatment	HR 1.05*; 95% CI 0.94, 1.19; p=0.393	DFS HR 1.00*; 95% CI 0.88, 1.14; p=1.00
	7 RCTs	NACT followed by local treatment vs local treatment - chemotherapy cycle lengths <14 days	HR 0.83*, 95% CI 0.69 to 1.00, p=0.046	
	11 RCTs	NACT followed by local treatment vs local treatment - chemotherapy cycle lengths ≥14 days	HR 1.25, 95% CI 1.07 to 1.46, p=0.005	
	11 RCTs	NACT followed by local treatment vs local treatment - cisplatin dose intensities ≥25mg/m^2/wk	HR 0.91*, 95% CI 0.78 to 1.05, p=0.20	
	7 RCTs	NACT followed by local treatment vs local treatment - cisplatin dose intensities <25mg/m^2/wk	HR 1.35, 95% CI 1.11 to 1.14, p=0.002	
	5 RCTs	NACT followed by surgery vs exclusive radiotherapy	HR 0.65*, 95% CI 0.53 to 0.80, p=0.0004	

*significant heterogeneity was reported for these results. CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; NACT=neoadjuvant chemotherapy; RCT=randomised controlled trial

Table 11 Survival outcomes reported in neoadjuvant chemotherapy RCTs

Study	Population	Groups	Overall survival		Disease-free/Progression-free survival	
				p-value		p-value
Katsumata 2013[76] RCT – JCOG 0102 Median follow-up 49 months	Stage IB2, IIA2 or IIB squamous cell carcinoma of the uterine cervix N=134 IB2: 36-39%	NACT followed by surgery (n=67)	5yr 70% (IB2: 78.4%; IIA2/IIB: 65.3%)	HR 1.07; 95% CI 0.54, 2.12; p=0.85	DFS 5yr 59.9% (IB2: 60.5%; IIA2/IIB: 59.3%)	HR 1.06; 95% CI 0.60, 1.88; p=0.85
		Radical hysterectomy (n=67)	5yr 74.4% (IB2: 82.9%; IIA2/IIB: 69.5%)		DFS 5yr 62.7% (IB2: 71.2%; IIA2/IIB: 58.4%)	
Wen 2012[77] RCT Mean follow-up 34.8 months	Stage IB2-IIA cervical cancer N=124 IB2: 26.7-38.7%	Intravenous NACT followed by radical surgery	3yr 82.9%	p=0.431	PFS 3yr 81.5%	p=0.354
		Intra-arterial NACT followed by radical surgery	3yr 80.4%		PFS 3yr 79.7%	
		Type III radical surgery	3yr 73.3%		PFS 3yr 70.7%	
		Brachytherapy followed by radical surgery	3yr 68.3%		PFS 3yr 66.3%	

CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; JCOG=Japan Clinical Oncology Group; NACT=neoadjuvant chemotherapy; PFS=progression-free survival; RCT=randomised controlled trial

Response to neoadjuvant chemotherapy

The systematic reviews did not report on response to chemotherapy as an outcome.

In the JCOG trial, the overall response (complete + partial response) rate was 70% (47 out of 67) on the investigators' assessment and 66% (44 out of 67) on independent central review.[76]

Wen et al (2012) reported that intra-arterial chemotherapy showed stronger response to neoadjuvant treatment than intravenous chemotherapy (partial response 79.3% vs 42.9% respectively; no clinical complete response was noted in either group).[77]

Recurrence

The systematic review by Kim et al (2013)[72] reported no differences in overall or loco-regional recurrences between treatments, however NACT was associated with lower rates of distant metastasis than primary surgery in RCTs and observational studies combined (7.8% vs 10.8%; OR 0.61; 95% CI: 0.42, 0.89; p=0.007) and RCTs (10.3% vs 15.8%; OR 0.61; 95% CI: 0.38, 0.97; p=0.04) but not in observational studies (p=0.14).

The review by Rydzewska et al (2012) reported that while there was some indication that NACT improved local and distant recurrence rates compared with primary surgery, due to differences in the effects between trials, these were no longer significant when the random-effects model was used.[73]

The RCT reported by Wen et al (2012) found there were no significant differences in the 3-year local (p=0.544) and distant (p=0.543) recurrence rates between the four treatment arms.[77]

Adverse events/toxicity

The systematic reviews did not report on adverse events or toxicity. The Cochrane review by Tierney et al (2004) did note that there was a relatively small number of late effects on the bladder, intestine or vagina recorded; with little to suggest that serious late toxicity is different between neoadjuvant chemotherapy followed by local treatment and local treatment alone.[74]

Haematological toxicity was reported in the NACT groups in both RCTs. In the trial reported by Wen et al (2012),[77] 62% and 79% of patients experienced haematological toxicity in the intravenous and intra-arterial neoadjuvant chemotherapy groups respectively (p=0.378), however the majority of these in both groups were grade 1 or 2. The JCOG 0102 trial reported that haematological toxicity grade 3 or 4 was more common in the NACT group than in those treated with primary surgery.[76]

The JCOG 0102 trial reported that non-haematological toxic effects (such as diarrhoea, bowel obstruction or urinary retention) were more common in the primary surgery group than in the NACT group. For those who received radiation following surgery or neoadjuvant chemotherapy, late adverse events (≥ 90 days after radiation) were significantly more common in the primary surgery group than the NACT group (65% vs 42%, respectively,

p=0.009). Early adverse events (within 90 days after radiation) were not significantly different between the groups (surgery: 70% vs NACT: 55%; p=0.108). The incidence of grade 3 or 4 lymphoedema was slightly higher in the NACT group than the primary surgery group.[76]

While there was some surgical morbidities reported in the JCOG 0102 trial (including ureteral or bladder injuries, wound infections and bowel obstructions), each were reported in less than 5% of patients.[76]

In the JCOG 0102 trial there was one treatment related death (<2%) in the NACT arm and three patients (<5%) discontinued chemotherapy treatment due to toxicity.[76] There were no treatment related deaths in the RCT reported by Wen et al (2012).[77]

Quality of life

Data on quality of life were not reported in any of the neoadjuvant chemotherapy studies.

Other reported outcomes

Operability

The review by Rydzewska et al (2012) and the updated results from the JCOG trial reported that there was no difference between treatment groups in rates of radical resection.[73, 76]

Pathological findings

Tumour diameters on pathological assessment were smaller in NACT groups compared with the surgery groups.[72, 76, 77] Lymph node metastasis was also lower in NACT groups.[72, 73, 76, 77]

Post-operative therapy

A smaller percentage of patients in the NACT groups needed to receive adjuvant radiotherapy/adjuvant therapy than in the primary surgery groups:

- Kim et al 2013[72] – all studies: 34.5% in NACT versus 53% in surgery groups received adjuvant radiotherapy; OR 0.57 (95% CI 0.33, 0.98); however this effect disappeared when RCTs and observational studies were analysed separately
- JCOG 0102[76] – 58% in NACT versus 79% surgery groups received adjuvant radiotherapy; p=0.015
- Wen et al 2012[77] – 76.8% in NACT versus 91.7% in local treatment groups received adjuvant therapy; p=0.027.

3.3.1 Summary

The systematic reviews and additional RCTs not included in the reviews identified on neoadjuvant chemotherapy reported inconsistent results with regards to survival. Individual trials reported no statistically significant differences between neoadjuvant chemotherapy and primary surgery groups. Pooled results reported in two systematic reviews indicated no statistically significant difference between neoadjuvant chemotherapy and primary surgery in one;[72] and a survival benefit following neoadjuvant chemotherapy in the other.[73] The third, older, systematic review by Tierney et al (2004)[74] reported that neoadjuvant chemotherapy

tended to improve survival in trials using chemotherapy cycle lengths shorter than 14 days or cisplatin dose intensities greater than 25 mg/m^2 per week. In contrast, neoadjuvant chemotherapy led to worse survival in trials using cycle lengths longer than 14 days or cisplatin dose intensities less than 25 mg/m^2 per week. In addition, neoadjuvant chemotherapy followed by surgery appeared to improve survival compared with exclusive radiotherapy. However, significant heterogeneity was noted in both the design and results of the trials.

No statistically significant differences in rates of recurrence were reported between neoadjuvant chemotherapy and primary surgery groups. Patients receiving neoadjuvant chemotherapy were more likely to experience haematological toxicity. No quality of life data were reported. Neoadjuvant chemotherapy was also reported to reduce tumour size and reduce the need for adjuvant radiotherapy.

3.3.2 Different neoadjuvant chemotherapy regimens

Study characteristics for the SNAP trials were previously reported in Table 9. The SNAP trials compared the three-drug combination of paclitaxel/ifosfamide/cisplatin (TIP) with two-drug combinations ifosfamide/cisplatin (IP)[85] or paclitaxel/cisplatin (TP).[86]

Survival

The SNAP 01 trial reported no significant difference in overall survival (HR 0.66; 95% CI 0.39, 1.10; p=0.11) or progression-free survival (HR, 0.75; 95% CI 0.48, 1.17; p=0.20) between the three-drug combination of paclitaxel/ifosfamide/cisplatin (TIP) with the two-drug combination ifosfamide/cisplatin (IP) regimens.[85] The trial also reported a multivariate analysis of assessment of treatment effect on overall survival and found a significant association by stage (HR 1.70; 95% CI 1.18, 2.44; p=0.004).[85]

Response to neoadjuvant chemotherapy

In the SNAP 01 trial,[85] a larger percentage of patients treated with TIP had an optimal response (complete or partial response) compared with those treated with IP (48% vs 23%, respectively, p=0.0004). Stage IB2 patients responded better to chemotherapy than those with higher stages:

- IB2 patients: 58% in TIP arm and 26% in IP arm had an optimal response
- IIA or IIB patients: 47% in TIP arm and 25% in IP arm had an optimal response
- III-IVA patients: 17% in TIP arm and 7% in IP arm had an optimal response.

Similarly, in the SNAP 02 trial,[86] a larger percentage of patients treated with TIP had an optimal response compared with those treated with TP (45% vs 30%, respectively).

Treatment compliance

In the SNAP 01 trial,[85] while similar percentages of patients completed their planned treatment (TIP: 94%; IP: 90%), a greater percentage of patients treated with TIP did so with

some dose adjustment or delay compared to those treated with IP (35% vs 18%, respectively).

Adverse events

Haematologic grade 3–4 toxicities were all statistically significantly more frequent on TIP compared with IP[85] or TP.[86]

In the SNAP 01 trial, nausea and vomiting were similar in both TIP and IP arms, however more patients in the TIP group experienced neurosensory symptoms.[85] Four (2%) deaths were reported as related to toxicity (three patients received the IP schedule and one patient received the TIP regimen).

Quality of life

Data on quality of life were not reported in any of the neoadjuvant chemotherapy studies.

3.3.2 Summary

Two phase II RCTs compared the three-drug combination of paclitaxel/ifosfamide/cisplatin (TIP) with two-drug combinations ifosfamide/cisplatin (IP) or paclitaxel/cisplatin (TP). No survival difference was reported between three-drug combination TIP and two-drug combination IP. Higher responses to neoadjuvant chemotherapy were observed with the three-drug combination, however this was also associated with more toxicity than either two-drug combination. No quality of life data were reported.

3.4 Fertility preservation procedures in women with stage IB2 cervical cancer

The following fertility preservation procedures were searched for using a separate literature search: ovarian transposition, transplantation or cryopreservation. In addition, case series on trachelectomy for treatment of stage IB2 cervical cancer were also included in this section (which were identified in main literature search but excluded from Research question 1 due to study design).

Although many papers were identified investigating the use of radical trachelectomy for management of cervical cancer, most of these were excluded as stage IB2 was not included in the studies (most of the studies required tumour size <2cm to be eligible for trachelectomy).

A systematic review on abdominal radical trachelectomy was identified,[138] however only one of the included studies had >10% stage IB2 patients.[115] Therefore, the original study has been included in the current review rather than the systematic review.

Two studies were identified on assisted conception following radical trachelectomy.[118, 121] The assisted conception methods discussed included oocyte and embryo cryopreservation and in vitro fertilization (IVF). The populations included in these studies were not clearly defined therefore it is uncertain whether stage IB2 cervical cancer patients were included.

Many other papers were identified on ovarian transposition, transplantation or cryopreservation but did not report on the pre-specified outcomes of interest (ie obstetric outcomes) for the current systematic review therefore these have not been included. These papers reported on preservation of ovarian function, however this was primarily to avoid the onset of menopausal symptoms rather than to preserve fertility. In addition, many of the studies identified on ovarian transposition were conducted in patients with hysterectomy, leaving surrogacy as the only option to conceive, however none of the studies identified explored this area.

Guidelines

The American Society of Clinical Oncology guidelines on fertility preservation for adults with cancer[132] includes presenting oocyte preservation as an "established fertility preservation method" and notes discussion of ovarian transposition where pelvic radiation therapy is performed as a cancer treatment, however there is only one specific recommendation regarding cervical cancer. It is suggested that radical trachelectomy (surgical removal of the uterine cervix) should be restricted to stage IA2 to IB cervical cancer with diameter <2cm and invasion <10mm. Other general recommendations from this guideline are included in Appendix E.

Summary of included papers

Six case series and one survey investigating trachelectomy were identified which include stage IB2 in the population.[109-117] An additional two case series[118, 119] and two surveys[120, 121] were identified investigating fertility preservation in populations including cervical cancer, however detailed information on which stages were included was not provided. One of the case series[118] and one survey[121] specifically reported on pregnancy outcomes following the use of assisted reproductive technology.

Quality assessment

Formal quality assessment was not performed for case series or surveys as they are considered a lower quality of evidence than comparative studies and standardised items for assessment are not available. It was noted that the populations in all of the studies were very small (≤40 patients).

Study characteristics

Characteristics of the fertility preservation studies are provided in Table 12. Two case series specifically included cervical cancers >2cm with 33%[110]–45%[109] stage IB2 included.

Some studies performed neoadjuvant chemotherapy prior to trachelectomy.[110, 112, 113] The case series reported by Vercellino et al (2012)[110] used neoadjuvant chemotherapy until the tumour was less than 2cm and therefore considered appropriate for fertility preserving surgery.

Patient selection criteria

To be eligible for trachelectomy patients required a strong desire to preserve fertility.[109, 110, 113, 115] Lintner et al (2013)[109] and Vercellino et al (2012)[110] required patients to be lymph node negative.[109] Additional eligibility criteria for trachelectomy in the case series by Vercellino et al (2012) included age <40 years, good performance status and adequate organ function. The surveys by Reh et al (2011)[121] and Carter et al[116, 117] included women aged 15-18 to 45 years.

Table 12 Characteristics of fertility preservation studies

Study	Population	Intervention	Outcomes
Lintner 2013[109] Case series	Cervical cancer IB1-IB2 >2cm N=31 IB2: 45%	Abdominal radical trachelectomy	Survival, recurrence, surgical outcomes, complications, pregnancy
Vercellino 2012[110] Case series	Stage I cervical cancer >2cm N=6 IB2: 33%	Neoadjuvant chemotherapy followed by radical vaginal trachelectomy	Surgical outcomes, relapse, pregnancy
van den Haak 2011[111] Case series, abstract	Early stage cervical cancer (IA2-IIA) N=29 IB2: not stated	Nerve-sparing radical abdominal trachelectomy	Pregnancy, recurrence
Robova 2010a[112]/Robova 2010b[113] Case series, Robova 2010b[113] abstract	Cervical cancer patients with tumours >2cm that had not infiltrated more than two thirds of the stroma N=15 IB2: not stated	High-dose-density NACT followed by SLN mapping and laparoscopic lymphadenectomy and vaginal simple trachelectomy	Recurrence, pregnancy
Mandic 2010[114] Case series, abstract	Cervical cancer stage IB N=12 IB2: not stated	Abdominal radical trachelectomy	Pregnancy
Ungar 2005[115] Case series	Cervical cancer (IA2-IB2) N=30 IB2: 17%	Abdominal radical trachelectomy	Surgical outcomes, recurrence, pregnancy
Carter 2011[116]/ Carter 2007[117] Survey	Early stage cervical cancer (IA1 with lymphovascular space involvement and IA2-IB2) N=33 (29 for 2007 paper) IB2: not stated	Radical trachelectomy	Psychosocial outcomes Reproductive concerns
Population – stage not defined			
Komatsu 2013[120] Survey	Cervical cancer (stage not defined) N=15 IB2: not stated	Radical trachelectomy	Experience of trachelectomy, psychosocial outcomes, pregnancy

Study	Population	Intervention	Outcomes
Wilde 2011[119] Case series, abstract	Early stage cervical cancer (stage not defined) N=40 (n=21 radical trachelectomy) IB2: not stated	Radical trachelectomy or radical cone biopsy	Recurrence, complications, pregnancy
Reh 2011[121] Survey	Female cancer patients (including cervical cancer, stage not defined) N=35 (n=10 cervical cancer) IB2: not stated	Fertility preservation	Treatment intentions, thoughts on fertility, QoL
Wong 2009[118] Case series	Women who had undergone assisted contraception following radical trachelectomy (implied after early stage cervical cancer, stage not defined) N=7 IB2: not stated	Assisted contraception following radical trachelectomy	Pregnancy

NACT=neoadjuvant chemotherapy; QoL=quality of life; SLN=sentinel lymph node

Outcomes

Survival and recurrence

Detailed survival data was reported in one case series of patients with cervical cancer >2cm treated with trachelectomy.[109] Five-year overall survival was 93.5%, two deaths had been reported, one in a patient with stage IB2 cervical cancer. Five-year disease-free survival was 87.1%.

Vercellino et al (2012) noted that at median follow-up of 2.55 years, no deaths or relapses had been recorded.[110] There was one death and three recurrences recorded in the Robova et al (2010) study.[112, 113]

Obstetric outcomes

Obstetric outcomes reported in the papers are presented in Table 13. All delivered babies (premature and full term) were healthy at time of discharge.

The rates of women who became pregnant ranged from 25%[119] to 60%[115] in studies explicitly stating number of women actively trying to conceive. In the studies not stating how many women were trying to conceive the rates are 20%[110, 120] to 73%[113] assuming that all women in the studies (other than those who lost fertility) were actively trying to conceive. For the studies investigating assisted conception the pregnancy rates were higher, ranging from 50% to 100%.[121] Miscarriage rates ranged from 0[110, 113] to 33%[114, 115] in the trachelectomy studies, and as high as 56%[118] in the assisted conception studies. Note that these rates are for small case series and generalisability is limited. Three studies reported that some patients lost fertility following trachelectomy.[110, 113, 115]

Assisted conception

The study by Wong et al (2009)[118] reported obstetric results from seven women who had undergone assisted conception following radical trachelectomy (implied after early stage cervical cancer, however stage was not defined). The assisted conception methods used included intrauterine insemination (IUI), in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). There were nine pregnancies reported overall, three in two women who had undergone IUI and six in four women who had undergone IVF. Of the nine pregnancies there were four live births (three pre-term), all in good health, and five miscarriages (three in the first trimester, two in the second trimester), see Table 14.

Reh et al (2011)[121] reported on a survey of a mixed population of female cancer patients (29% cervical cancer) presenting to a fertility clinic for counselling and/or treatment. Overall, 89% of the study population pursued assisted reproduction, 34% before cancer treatment, and 54% after treatment. While the ovarian reserve testing at baseline was similar between groups, significantly more oocytes were retrieved (p=0.003) and more gametes frozen (p=0.03) in the before-treatment group compared with the after-treatment group. It was noted that five patients in the after-treatment group had at least one cycle cancelled for poor ovarian response.

In the before-treatment group,[121] 11 patients completed oocyte or embryo cryopreservation cycles resulting in a total of 153 cryopreserved oocytes and 38 cryopreserved embryos. Three patients returned after completing cancer treatment to attempt pregnancy using thawed frozen embryos. Two full-term deliveries were achieved, one using a sister-gestational carrier. One patient had a miscarriage after two thaw cycles. No patient returned to use cryopreserved oocytes.

In the after-treatment group,[121] 11 patients were still undergoing cancer treatment and completed oocyte and/or embryo cryopreservation cycles resulting in a total of 111 cryopreserved oocytes and 23 cryopreserved embryos. To date no patients have returned to use their frozen gametes. An additional eight patients were seeking immediate pregnancy after completion of cancer therapy and underwent cycles of IVF. Obstetric outcomes of these eight patients are summarised in Table 14, with five pregnancies in four women including one miscarriage, two full term births and two ongoing pregnancies.

Table 13 Obstetric outcomes reported in fertility preservation papers

Study Follow-up	ART/VRT	N (IB2)	Lost fertility	Trying to conceive	Pregnancies/ women	Miscarriage	Delivery		Ongoing pregnancy	Undergoing fertility treatment
							Premature	Term		
Lintner 2013[109] 90mths	ART	31 (14)		8	4/3	1	1	2		1
Vercellino 2012[110] 30.6mths	VRT	6 (2)	1		1/1			1		
Van den Haak 2011[111] 42mths	ART	29		16	11/6	2		9		5*
Robova 2010b[113] Not stated	VRT	15	4	Not stated	8/8		1	6	1	
Mandic 2010[114] 39.6mths	ART	12			3/3	1	2			1¥
Ungar 2005[115] 47mths	ART	30 (5)	2	5€	3+/3	1		2		
Komatsu 2013[120] Not stated	Radical trachelectomy	15 (INA)		Not stated	3/3		3β			8
Wilde 2011[119] 16mths	Radical trachelectomy	40 (INA)		28	8/7	1 (abortion)	4β		3	

*one for male infertility; ¥one failure of IVF procedure; €this study recommended patients wait for two years following procedure before attempting to conceive; +one IVF pregnancy; βlive births, not stated if premature or at term. ART=abdominal radical trachelectomy; INA=information not available; IVF=in vitro fertilisation; VRT=vaginal radical trachelectomy

Table 14 Obstetric outcomes reported in assisted conception papers

Study	Assisted conception method	Trying to conceive	Pregnancies/women	Miscarriage	Live birth		Ongoing pregnancy
					Premature	Term	
Wong 2009[118]	IUI	2	3/2	1	1	1	
	IVF	4	6/4	4	2		
	IVF/ICSI	1	0				
Reh 2011[121]	Before-treatment group: use of frozen embryos	3	3/3	1		2	
	After-treatment group: IVF	8	5/4	1		2*	2

*One case was a healthy twin delivery using donor oocytes. ICSI=intracytoplasmic sperm injection; IUI= intrauterine insemination; IVF=in vitro fertilisation;

Adverse events

Limited adverse event information has been reported in the fertility preservation papers. Five case series and one survey provided adverse event information.

Lintner et al (2013)[109] reported the following events:

- 1 intraoperative one-sided ureteric injury
- 1 case of cervical stenosis
- 1 case of stenosis of both ureters
- 5 cases of transient urinary retention
- 4 cases of constipation

No cases of lymphoedema were reported.

Vercellino et al (2012)[110] reported that no intraoperative complications occurred.

Wilde et al (2011)[119] reported that the perioperative complication rate was 2.5%, that there were 14 postoperative complications in 10 women (25%) but that there were no bladder or urethral injuries.

In the survey reported by Carter et al (2011),[116] 19 (58%) of patients indicated they had had a problem since surgery by 3 months, this lessened to 36% by 24 months. The types of issues that had been reported included menstrual/vaginal issues, general pain, recovery, sexual issues, bowel/bladder issues and swelling/lymphoedema.

Robova et al (2010a)[112] reported five cases of neutropenia, with no other toxicity reported.

Ungar et al (2005)[115] reported that intraoperative complications were rare with only one unilateral ureteral injury occurring. Voiding difficulties were common however these resolved within two to three weeks.

Quality of life/psychosocial outcomes

Quality of life and/or psychosocial outcomes were not reported in any of the case series on trachelectomy.

Three surveys were identified which explored psychosocial outcomes of fertility preserving surgery in women with cervical cancer.[116, 117, 120, 121]

Fertility concerns

All three surveys discussed fertility concerns.

At the time of surgery, Reh et al (2011)[121] reported that 52% of female cancer patients felt that having a child was 'most important' in their life and 62% were 'most concerned' with the impact their cancer treatment would have on fertility. These opinions still held in the 1-year follow-up survey.

Carter et al (2011)[116] surveyed women over 24 months following trachelectomy for early cervical cancer and found that at each time point over 70% reported concerns about trying to conceive, however this slightly lessened with time with 88% expressing concerns at 6 months to 73% at 24 months.

Komatsu et al (2013)[120] reported that women associated their cervical cancer diagnosis with 'awakening femininity', reflecting on their own fertility and considering perceptions of themselves with or without a uterus. Following trachelectomy, a range of views were expressed, some women viewed a stronger determination to have a child, while others decided that their priorities had changed and that motherhood was now not as important for them.

Assisted conception

Reh et al (2011)[121] reported that most women expressed strong preferences in assisted conception procedures using autologous rather than donated oocytes. Fifty-four per cent were unsure regarding the level of risk they were willing to undertake to pursue fertility treatment, 19% were willing to undertake a minimal risk and 19% a moderate risk. Eight per cent (two patients) were willing to do 'whatever it takes' to conceive a child.

In the survey by Carter et al (2011),[116] by 24 months after surgery, 15–18% of women had sought reproductive assistance by speaking with an infertility specialist.

The survey by Komatsu et al (2013)[120] found that while some women were ready to attempt assisted conception, others wished to conceive naturally.

Other concerns

Fear of recurrence

Carter et al (2007)[117] reported that concern about recurrence was acknowledged by 90% of women, with 75% rating their level of worry as high. These concerns persisted up to 6 months after surgery. Komatsu et al (2013)[120] also reported on fears of recurrence, with some women avoiding sexual activity because of this.

Health of baby

In the surveys by Komatsu et al (2013)[120] and Carter et al (2007),[117] some women expressed concerns that if they were to conceive that the baby may be unhealthy following cancer treatment.

Pressure to conceive

Komatsu et al (2013)[120] reported that one woman felt under pressure from her healthcare provider to fall pregnant.

An earlier report by Carter et al (2007)[117] also noted women feeling time pressure to conceive.

Overall quality of life

Reh et al (2011)[121] reported that the FACT-B scores for physical, emotional, additional, social and functional categories were positive overall. Scores were not significantly different across categories at the 1-year follow-up survey except for social scores which were significantly higher at the 1-year follow-up survey than at time of treatment.

Carter et al (2011)[116] reported five primary themes for difficulties and/or hardest adjustments: menstrual or vaginal issues, emotional impact, life interruptions/return to normalcy, general pain and recovery process. In the earlier report from this survey,[117] all patients expressed mild

to moderate levels of stress at the preoperative assessment, decreasing to 81% at 3 and 6 months after surgery.

3.4 Summary

Thirteen papers were identified on fertility preservation in populations thought to include stage IB2 cervical cancer (although percentages were often not reported). No comparative studies were identified, only small case series and surveys. It was noted that many other studies on trachelectomy were identified which excluded patients with tumours >2cm and therefore were not included in this review. One paper demonstrated the feasibility of trachelectomy specifically in larger tumours (>2cm). Successful full term pregnancies following trachelectomy have been reported in a number of papers, however rates of miscarriage were high in some studies. Two papers reported successful full term pregnancies following assisted conception after trachelectomy. Fertility concerns were common in women considering or undertaking trachelectomy. Following surgery, women were often concerned about recurrence, health of any future babies and pressure to conceive. No papers were identified on fertility outcomes following ovarian transposition in populations including stage IB2 cervical cancer.

3.5 Ongoing trials

The following clinical trials sites were searched to identify relevant ongoing trials regarding the management of stage IB2 cervical cancer:

- Clinicaltrials.gov
- WHO International Clinical Trials Registry Platform.

Ongoing trials identified are described in Table 19. Most of the trials are not expected to be completed before 2018. Three RCTs were identified comparing primary surgery with primary chemoradiotherapy, however one of these trials has been terminated (while reasons for termination were not described in the clinical trials record, another paper, Hacker et al (2013),[130] mentions termination of this trial was due to failure to accrue). A trial on completion surgery was identified, however this was also terminated due to low accrual. Four RCTs were identified comparing neoadjuvant chemotherapy followed by surgery with chemoradiotherapy, one of which will also be evaluating the use of neoadjuvant chemoradiotherapy. One trial was identified comparing different methods of hysterectomy and another was identified on surgical staging compared with radiologic staging of cervical cancer.

Note ongoing trials reported in this section relate to the topics included in the systematic review. Ongoing trials investigating other management options such as chemotherapy/radiotherapy combinations (not including surgery or neoadjuvant chemotherapy) have not been included here. Two ongoing trials which were outside the topics as presented in the review (therefore not included in the table below) but were noted include the OUTBACK trial,[139] which is an Australian trial investigating adjuvant chemotherapy following chemoradiotherapy as primary treatment compared to chemoradiotherapy alone and the INTERLACE trial[140] which is a UK trial comparing induction chemotherapy followed by chemoradiotherapy with chemoradiotherapy alone.

Table 15 Ongoing trials investigating management strategies for stage IB2 cervical cancer

Trial ID & Location	Study design & Status*	Participants	Intervention	Control	Outcome measures
Primary surgery					
KGOG 1029[141] Korea	RCT Currently recruiting Estimated primary completion: July 2020	Stage IB2 and IIA2 cervical cancer Target N=409	Primary surgery with tailored adjuvant therapy	Primary CRT	5yr OS, PFS, recurrence, toxicity, QoL
DRKS00004800[142] Germany	RCT Recruitment pending	Stage IB2 or IIB cervical cancer Target N=328	Primary surgery	Primary CRT	5yr OS, DFS, local control rate, QoL, toxicity

Trial ID & Location	Study design & Status*	Participants	Intervention	Control	Outcome measures
GOG-0201[143] Japan, US	RCT Terminated	Stage IB2 cervical cancer	Primary surgery	CRT	N/A
Completion surgery					
GYNECO 02/0108[144] France	RCT Terminated (low accrual)	Stage IB2/II cervical cancer	CRT followed by hysterectomy	CRT	OS, RFS
Hysterectomy surgical techniques					
NCT01886508[145] China	RCT Recruitment pending	Stage IA2, IB1, IIA1 and IB2, IIA2 after NACT Target N=240	Nerve-sparing RH	RH	Urodynamic outcomes
Neoadjuvant chemotherapy					
EORTC-55994[146] Europe	RCT Currently recruiting Estimated study completion: Apr 2018 (primary completion Jun 2014)	Stage IB2, IIA (>4cm) or IIB cervical cancer Target N=686	NACT followed by surgery	Concomitant CRT	OS, PFS, QoL, toxicity
TGOC-03[147] Thailand	RCT Currently recruiting Estimated study completion: Jun 2018 (primary completion Sep 2013)	Stage IB2-early IIB cervical cancer Target N=824	NACT followed by surgery	Concurrent CRT	OS, DFS
NCT00193739[148] India	RCT Recruitment status unknown Estimated study completion: Sept 2010	Stage IB2-IIB cervical cancer Target N=730	NACT followed by surgery	Concurrent CRT	OS, DFS, morbidity, distant metastases
GRHCO-01[149] India	RCT Not yet recruiting Estimated study	Early stage bulky cervical cancer (stage IB2, IIA2 and IIB)	i) NACT followed by surgery ii) NACRT followed by	Concurrent CRT	OS, DFS, adverse effects, QoL

Trial ID & Location	Study design & Status*	Participants	Intervention	Control	Outcome measures
	completion: Aug 2018	Target N=180	surgery		
Investigative procedures to stage cervical cancer					
LiLACS[150] US	RCT Recruitment pending	Stage IB2-IVA cervical cancer Target N=600	Pre-therapeutic laparoscopic surgical staging followed by tailored CRT	PET/CT radiologic staging alone followed by CRT	OS, DFS, morbidity

CRT=chemoradiotherapy; CT=computed tomography; DFS=disease-free survival; N/A=not applicable; NACRT=neoadjuvant chemoradiotherapy; NACT=neoadjuvant chemotherapy; OS=overall survival; PET=positron emission tomography; PFS=progression-free survival; QoL=quality of life; RCT=randomised controlled trial; RFS=relapse-free survival; RH=radical hysterectomy

*PRIMARY COMPLETION DATE: The date that the last participant in a clinical study was examined or received an intervention and that data for the primary outcome measure were collected. Whether the clinical study ended according to the protocol or was terminated does not affect this date. The "estimated primary completion date" is the date that the researchers think will be the primary completion date for the study.[151]

*STUDY COMPLETION DATE: The date that the final data for a clinical study were collected because the last study participant has made the final visit to the study location (that is, "last subject, last visit").[151]

4 Discussion

In this systematic review about management strategies for women with stage IB2 cervical cancer, over 140 papers were reviewed. There were a limited number of studies only including stage IB2 patients or stratifying results by stage, therefore it is difficult to assess the impact of treatment specifically on stage IB2 cervical cancer. Studies differed in categorisations of populations which included stage IB2 cervical cancer, and it was sometimes included within the definition of early cervical cancer, sometimes as locally advanced cervical cancer. The research questions focused on the effectiveness of various interventions to manage stage IB2 cervical cancer. As the effectiveness of chemoradiotherapy compared with radiotherapy alone has been demonstrated in a number of randomised controlled trials (RCTs),[6] this review focused primarily on surgery and neoadjuvant chemotherapy. While any quality of life and/or psychosocial outcomes reported in the studies were recorded, the psychological impact of treatment decisions was not specifically searched for.

Surgery

Only one RCT was identified which compared primary surgery to primary radiotherapy.[7] While this RCT provided long-term survival data, it was reported in abstract only. This trial showed no survival differences between groups, however the comparison group is now considered to be outdated, with concurrent chemoradiotherapy being the most commonly recommended treatment approach (rather than radiotherapy alone). Two RCTs comparing primary surgery to primary chemoradiotherapy for IB2-IIB patients are currently underway.[141, 142] The remaining retrospective studies reported inconsistent results on survival, with either no difference reported or improved survival following primary surgery. Of four studies including only stage IB2 cervical cancer patients, although survival rates appeared higher in the primary surgery groups, three studies showed no statistically significant survival difference between primary surgery and primary radiotherapy/chemoradiotherapy.[15, 18, 19] The other study reported a significant improvement in survival with primary surgery compared with primary radiotherapy.[11] Another trial including >75% stage IB2 patients also showed a significant survival improvement with primary surgery compared with primary chemoradiotherapy however this was borderline statistically significant (p=0.048).[9] One large retrospective study (abstract only) reported that compared with primary radiotherapy, radical hysterectomy improved survival for tumours 4-6cm, but this improvement was not observed for tumours greater than 6cm.[16]

There were a limited number of studies comparing the use of trachelectomy with hysterectomy in populations including stage IB2 cervical cancer as these patients were often not considered appropriate for trachelectomy. While indications for trachelectomy usually require tumour size to be less than 2cm in diameter, a recent case series by Lintner et al (2013)[109] has demonstrated the feasibility of trachelectomy in patients with tumours greater than 2cm in diameter (see Fertility preservation section). Of the three identified studies, two were reported as abstracts only, and none of the studies explicitly stated the percentage of stage IB2 patients included. Of the limited outcomes that were reported, no differences for survival, recurrence, sexual dysfunction or quality of life between trachelectomy and hysterectomy were reported. No fertility outcomes were reported in the comparative studies.

Seven studies, including three RCTs, were identified which investigated the addition of hysterectomy following primary radiotherapy/chemoradiotherapy (completion surgery). The percentage of stage IB2 cervical cancer patients included in the studies ranged from 16%[26] to 100%.[29, 33] Six studies reported on survival with all studies consistently reporting that the addition of completion surgery did not appear to have any survival benefit compared with radiotherapy/chemoradiotherapy alone. Completion surgery may reduce the risk of recurrence (particularly distant metastases), however results were inconsistent between studies.

A number of papers were identified which compared different surgical methods for performing radical hysterectomy, the most common comparisons being between open/abdominal hysterectomy, laparoscopic hysterectomy and robotic hysterectomy. Limited information on survival and recurrence outcomes were reported. Open/abdominal radical hysterectomy appeared to have worse surgical outcomes and adverse events than robotic hysterectomy. Most studies reported no significant difference in surgical outcomes between robotic and laparoscopic hysterectomy. However, there were a limited number of RCTs identified and the systematic reviews only included papers published up to 2009/2010. None of the systematic reviews or RCTs stated how many stage IB2 patients were included in the populations. One review noted that studies on robotic surgery may be biased, with underreporting of failures and adverse events.[62]

Neoadjuvant chemotherapy

Three high quality systematic reviews were identified which reported on the effectiveness of neoadjuvant chemotherapy followed by surgery to manage early/locally advanced cervical cancer. However, strong conclusions from pooled results are limited due to heterogeneity between primary studies. Two reviews reported different conclusions following meta-analysis of similar data; one reporting no survival differences between neoadjuvant chemotherapy and primary surgery,[72] the other reporting a survival benefit in the neoadjuvant chemotherapy group.[73] Individual results from RCTs tended to show no statistically significant difference in survival between neoadjuvant chemotherapy and primary surgery groups. The third, older, systematic review[74] included a broader range of neoadjuvant chemotherapy comparisons (neoadjuvant chemotherapy followed by local treatment versus local treatment alone; and neoadjuvant chemotherapy followed by surgery versus exclusive radiotherapy) and reported significant heterogeneity between trials. This review suggested that neoadjuvant chemotherapy tended to improve survival in trials using chemotherapy cycle lengths shorter than 14 days or cisplatin dose intensities greater than 25 mg/m^2 per week; however, neoadjuvant chemotherapy led to worse survival in trials using cycle lengths longer than 14 days or cisplatin dose intensities less than 25 mg/m^2 per week. Four ongoing RCTs were identified, including EORTC-55994,[146] which will compare neoadjuvant chemotherapy followed by surgery with primary chemoradiotherapy. These trials are not expected to be completed before 2018 and results are awaited with interest.

Fertility preservation

No comparative studies were identified which reported obstetric outcomes following fertility preservation methods and included stage IB2 cervical cancer patients. Many trachelectomy studies were identified which only included patients with tumour size <2cm in diameter, and therefore were not included in this review. In the included studies, detailed patient eligibility criteria was often not reported (other than a strong desire to preserve fertility). Two studies used neoadjuvant chemotherapy prior to trachelectomy, in one study this was specifically to

reduce the tumour size to <2cm before performing the surgery. An additional eligibility requirement in two case series included lymph node negativity. Although data for this section were from small case series, a number of successful pregnancies following trachelectomy in populations including larger tumours have been reported.

Studies identified on ovarian transposition focused on the retention of ovarian function specifically to avoid menopausal symptoms rather than to preserve fertility, and were therefore not included. Many of the patients who underwent ovarian transposition also had radical hysterectomy. While these patients would not be able to become pregnant, if ovarian function remained intact, surrogacy should remain a viable option. However, surrogacy was not explored in any of the identified studies.

Ongoing trials

A number of ongoing RCTs were identified, particularly with regards to primary surgery and neoadjuvant chemotherapy. The trials include a range of cervical cancer stages, however many focus on the management of bulky early stage cervical cancer, and compare interventions with standard chemoradiotherapy which should provide clinicians with better evidence to suggest optimal management options for these patients. Although many of the trials have an estimated study completion of 2018 or later, primary analyses of results may be available prior to this time. It was noted that two trials on surgery (one primary surgery, one completion surgery) were terminated early due to low accrual, however further explanation of this was not available.

5 Conclusion

A previous Cochrane review has reported that chemoradiotherapy is more effective than radiotherapy alone for women with cervical cancer, as demonstrated in a number of RCTs.[6] While there are no Australian guidelines for the management of cervical cancer, in other international guidelines, concurrent chemoradiotherapy is most commonly recommended as the primary treatment for women with stage IB2 cervical cancer. This current review focuses on the evidence for other treatment options, including primary surgery and neoadjuvant chemotherapy, to manage stage IB2 cervical cancer.

Over 140 papers have been considered in the current systematic review. Data from high quality systematic reviews and RCTs were available for some, but not all, topics identified. There were a limited number of studies only including stage IB2 patients or stratifying results by stage, therefore it is difficult to assess the impact of treatment specifically on stage IB2 cervical cancer.

The current systematic review found that multiple treatment options, including concurrent chemoradiotherapy, primary surgery, and neoadjuvant chemotherapy followed by surgery, are effective at managing stage IB2 cervical cancer. It is not clear whether there are survival benefits with one treatment compared with another. Therefore it is difficult to determine which is the optimal treatment based on current available evidence. Patient factors and patient/physician preference are likely to influence treatment choice. Ongoing trials comparing various treatment options with the current standard concurrent chemoradiotherapy will report in the next few years and may further guide management of these patients.

Appendix A Contributors

Working Group members

Management of women with stage IB2 cervical cancer with treatments other than chemoradiotherapy: a systematic review was developed with input from an expert multidisciplinary Working Group with the following members:

- A/Professor Orla McNally (Chair) Gynaecological Oncology
- A/Professor Philip Beale Medical Oncology
- Ms Isobel Black Nursing
- Dr Robyn Cheuk Radiation Oncology
- Ms Kathryn Crisell Consumer Representative
- Dr Gregory Gard Gynaecological Oncology
- A/Prof Kailash Narayan Radiation Oncology
- Dr Kate Stern Fertility Specialist

Cancer Australia staff

The following Cancer Australia staff were involved in the development of *Management of women with stage IB2 cervical cancer with treatments other than chemoradiotherapy: a systematic review*

- Ms Jennifer Chynoweth General Manager, Cancer Care, Project Sponsor
- Ms Jane Francis Manager, Gynaecological Cancers
- Ms Charmaine Larment Senior Project Officer
- Mr Stephen Evans Project Officer
- Mr Paul Cramer General Manager, Programs, Project Sponsor
- Ms Phillipa Hastings Senior Project Officer
- Dr Simone DeMorgan Senior Project Officer, Research

Appendix B Cervical cancer stages[152]

Staging cervical cancer (TNM and International Federation of Gynecology and Obstetrics [FIGO])

Primary tumor (T)			
TNM categories	**FIGO stages**	**Definition**	
TX		Primary tumor cannot be assessed	
T0		No evidence of primary tumor	
Tis*		Carcinoma in situ (preinvasive carcinoma)	
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)	
T1a•	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.	
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread	
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm in depth with a horizontal spread 7.0 mm or less	
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2	
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension	
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension	
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina	
T2a	IIA	Tumor without parametrial invasion or involvement of the lower one-third of the vagina[1,2]	
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension with involvement of less than the upper two-thirds of the vagina	
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension with involvement of less than the upper two-thirds of the vagina	
T2b	IIB	Tumor with parametrial invasion	
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney	
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall	
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney	
T4	IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)	
Regional lymph nodes (N)			
TNM categories	**FIGO stages**	**Definition**	
NX		Regional lymph nodes cannot be assessed	
N0		No regional lymph node metastasis	
N1		Regional lymph node metastasis	
Distant metastasis (M)			
TNM categories	**FIGO stages**	**Definition**	
M0		No distant metastasis	
M1	IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)	
Anatomic stage/prognostic groups			
Stage 0*	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IA1	T1a1	N0	M0
Stage IA2	T1a2	N0	M0
Stage IB	T1b	N0	M0
Stage IB1	T1b1	N0	M0
Stage IB2	T1b2	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIA1	T2a1	N0	M0
Stage IIA2	T2a2	N0	M0
Stage IIB	T2b	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	Any N	M0
	T1-3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Note: cTNM is the clinical classification, pTNM is the pathologic classification.
* FIGO no longer includes Stage 0 (Tis).
• All macroscopically visible lesions-even with superficial invasion-are T1b/IB.

References:
1. *Pecorelli S. Revised FIGO staging for carcinoma of the cervix. Int J Gynecol Obstet 2009; 105:107.*
2. *Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynecol Obstet 2009; 105:103.*

Appendix C PICO criteria for research questions

Research question 1

What is the effectiveness of surgery in the management of women with stage IB2 cervical cancer?

Participants: women with stage IB2 cervical cancer

Interventions/Comparisons: surgery compared to other surgery or non-surgical treatments including chemoradiation and radiation

Outcomes: overall survival, disease/progression free survival, recurrence, quality of life/adverse events/toxicity, fertility outcomes

Research question 2

What is the effectiveness of neoadjuvant chemotherapy in the treatment of women with stage IB2 cervical cancer?

Participants: women with stage IB2 cervical cancer

Interventions/Comparisons: neoadjuvant chemotherapy before surgery or before chemoradiation/radiation, or both, in comparison with surgery alone or chemoradiation/radiation alone or surgery and chemoradiation/radiation

Outcomes: overall survival, disease/progression free survival, response to chemotherapy, recurrence, quality of life/adverse events/toxicity

Research question 3

What is the effectiveness of fertility preservation procedures in women with stage IB2 cervical cancer?

Participants: women with cervical cancer

Interventions/Comparisons: fertility preservation procedures such ovary trans-position, embryo cryopreservation, oocyte cryopreservation and ovarian cryopreservation

Outcomes: successful full-term pregnancy, adverse events, quality of life/psychosocial

Note: This research question was searched for using a separate search that was not limited by study type or specific stage terms. Papers identified in Research question 1 investigating fertility-sparing surgery were included in this research question.

Additional areas of interest

Additional area 1

What is the effectiveness of investigative procedures in assessing stage to determine management of early-stage cervical cancer?

Participants: women with newly diagnosed early (stage I) cervical cancer

Interventions/Comparisons: clinical examination; imaging techniques such as MRI, CT, PET scans; and surgical procedures such as sentinel lymph node biopsy and laparoscopic staging

Outcomes: Improved accuracy of staging, treatment decisions

Note: This topic was searched for using a non-systematic approach; all relevant results identified in papers sourced for other research questions were noted. A separate search (non-systematic) was conducted.

Additional area 2

What is the influence of the length of time to treatment on outcomes for women with stage IB2 cervical cancer?

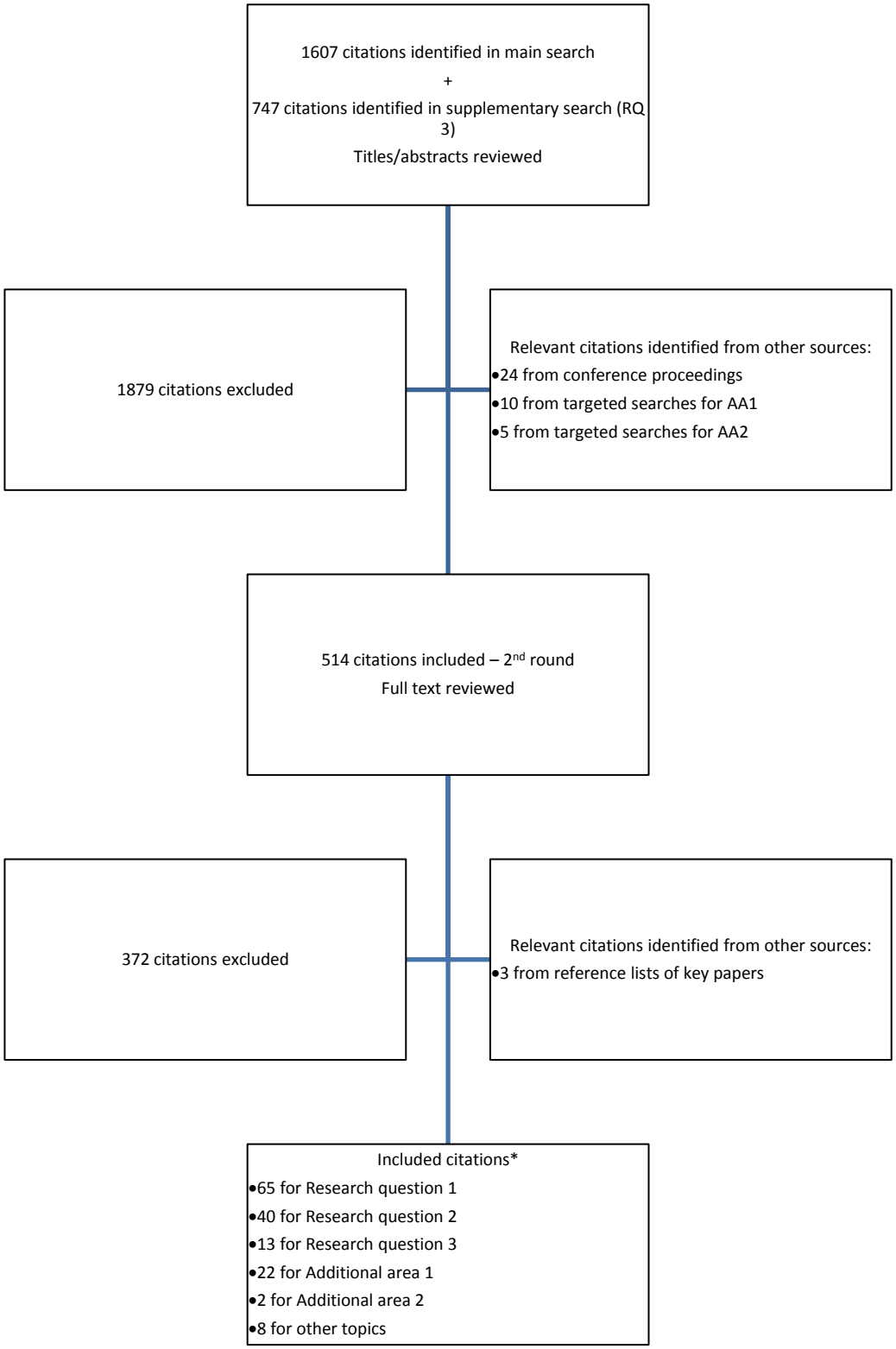
Participants: women with stage IB2 cervical cancer

Interventions/Comparisons: varied lengths of time between diagnosis and start of treatment

Outcomes: overall survival, disease/progression free survival, quality of life /adverse events/toxicity, psychosocial outcomes

Note: This topic was searched for using a non-systematic approach; all relevant data identified in papers sourced for other research questions were noted. A separate search (non-systematic) was conducted.

Appendix D Inclusion/exclusion flowchart



*Note some citations are identified in multiple sections
AA=additional area; RQ=research question

Appendix E International cervical cancer guidelines

Organisation/CPG title/Year	Key recommendations
National Cancer Comprehensive Network (NCCN) Clinical Practice Guidelines in Oncology: Cervical Cancer (2013)[1]	• Primary treatment: Concurrent chemoradiation, using cisplatin-based chemotherapy (either cisplatin alone or cisplatin/5-FU), is the treatment of choice for stages IB2, II, III and IVA disease based on the results of 5 randomised clinical trials. • For stage IB2 and IIB tumors, the panel had a major disagreement about recommending adjuvant hysterectomy (also known as completion surgery) after primary chemoradiation. • Neoadjuvant chemotherapy is not recommended. • Radiologic imaging is recommended for assessing stage IB2 tumors.
Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2012)[2]	• Primary treatment: Combination chemotherapy (CT)/radiation therapy (RT) with cisplatin for Stage IB2, IIB–IV based on five randomised trials and Cochrane meta-analysis. Concurrent carboplatin or nonplatinum chemoradiation regimens are options for patients who may not tolerate cisplatin-containing schedules. • Systemic consolidation with adjuvant chemotherapy following chemoradiation should only be used in clinical trials • Neoadjuvant chemotherapy followed by radical surgery could have an important role in the treatment of locally advanced cervical cancer, but the appropriate indications still need to be established. • Women with risk factors on the pathology specimen should receive adjuvant therapy following hysterectomy. 1) Intermediate risk of relapse: A benefit demonstrated for postoperative radiotherapy in women with the following features: deep cervical stromal invasion (to the middle or one-third depth), lymphovascular space invasion, and large tumor size (>4 cm). 2) High risk of relapse: A benefit demonstrated for adjuvant chemoradiation in women with the following features: one or more factors such as positive or close surgical margins, positive lymph nodes, or microscopic parametrial involvement.
National Institute for Health and Clinical Excellence (NICE) Laparoscopic radical hysterectomy for early cervical cancer (stages I-IIA) (Interventional procedure guidance)	• Early stage cervical cancer (Stage I-IIA) is usually treated by radical hysterectomy. Radiotherapy may be used, with or without surgery, and is usually combined with chemotherapy. More advanced cervical cancer is generally treated with radiotherapy and chemotherapy. • This document also provides an outline of the procedure, efficacy and safety of the procedure.

Organisation/CPG title/Year	Key recommendations
(2010)[122]	
National Institute for Health and Clinical Excellence (NICE) High dose brachytherapy for carcinoma of the cervix (2006) (Interventional procedure guidance)[123]	• Cancer of the cervix can be treated with surgery, radiotherapy, chemotherapy or a combination of these treatments. Surgery is often the main treatment for cancer of the cervix in its early stages (where cancer is found only in the cervix). Chemotherapy is occasionally used before surgery, shrinking the cancer to make the operation simpler. However, it is mainly given in combination with radiotherapy, either as a primary therapy or after surgery. • Brachytherapy can be given in low, medium or high dose rates. Low dose rate brachytherapy delivers radiation slowly. In order to administer a radiation dose that will eliminate the cancer, applicators need to be in place in the vagina for 2 to 3 days.
Scottish Intercollegiate Guidelines Network. Management of cervical cancer. A national clinical guideline (2008)[3]	• Generally chemoradiotherapy is used to treat women with FIGO IB2, IIA, IIB, IIIA, IIIB and IVA disease. Surgery is not offered to this group of women because of the significant risk of positive margins and positive nodes. • Any patient with cervical cancer considered suitable for radical radiotherapy treatment should have concurrent chemoradiotherapy with a platinum based chemotherapy, if fit enough. • Patients who have undergone surgery for cervical cancer and have positive lymph nodes should be considered for adjuvant treatment with concurrent chemoradiotherapy. • No data from RCTs were identified describing the value of using neoadjuvant chemotherapy to make large inoperable tumours surgically resectable.
ACR Appropriateness Criteria® advanced cervical cancer. American College of Radiology. (2010) NGC:008485 (Stage IB or greater)[153]	• The preferred modality for treating advanced cervix cancer (Stage IB or greater) is chemoradiotherapy.
ACR Appropriateness Criteria's Definitive Therapy for Early-Stage Cervical Cancer. American College of Radiology (2012)[4]	• Consensus supports the use of chemoradiotherapy as the preferred treatment modality for tumors above stage IB1 • There are no clear guidelines as to when, or in whom, RT or chemoradiotherapy should be followed by extrafascial hysterectomy. This remains an area of active investigation. • The appropriateness of induction chemotherapy followed by surgery remains uncertain, and it should be performed only in the context of a clinical trial • Until more data are collected, adjuvant chemotherapy may be most

Organisation/CPG title/Year	Key recommendations
	appropriately used in the setting of a clinical trial
Cancer Care Ontario Primary Treatment for Locally Advanced Cervical Cancer: Concurrent Platinum-based Chemotherapy and Radiation (2004)[5]	• Women with cervical cancer for whom treatment with radiotherapy is being considered (described below) should be offered concurrent cisplatin with their course of radiotherapy. • Women with cervical cancer for whom primary treatment with radiotherapy is being considered: - those with locally advanced cervical cancer, - those with bulky clinical stage IB (>4 cm) cervical cancer, who are treated with radiotherapy, - those with high-risk early-stage cervical cancer (node-positive or margin-positive), who will be treated with radiotherapy following hysterectomy.
American Society of Clinical Oncology. Fertility preservation for patients with cancer (2013)[132]	• Discuss fertility preservation with all patients of reproductive age (and with parents or guardians of children and adolescents) if infertility is a potential risk of therapy • Refer patients who express an interest in fertility preservation (and patients who are ambivalent) to reproductive specialists • Address fertility preservation as early as possible, before treatment starts • Refer patients to psychosocial providers if they experience distress about potential infertility • Present both embryo and oocyte cryopreservation as established fertility preservation methods • Discuss the option of ovarian transposition (oophoropexy) when pelvic radiation therapy is performed as cancer treatment • Inform patients of conservative gynecologic surgery and radiation therapy options. o Specific to cervical cancer: It has been suggested that radical trachelectomy (surgical removal of the uterine cervix) should be restricted to stage IA2 to IB cervical cancer with diameter <2 cm and invasion <10 mm • Inform patients that there is insufficient evidence regarding the effectiveness of ovarian suppression (gonadotropin-releasing hormone analogues) as a fertility preservation method, and these agents should not be relied on to preserve fertility • Inform patients that other methods (eg, ovarian tissue cryopreservation, which does not require sexual maturity, for the purpose of future transplantation) are still experimental.

ACR=American College of Radiology; CPG=clinical practice guideline; CT=computed tomography; ESMO=European Society of Medical Oncology; FIGO= Féderation Internationale de Gynécologie et d'Obstétrique;

NCCN=National Comprehensive Cancer Network; NICE=National Institute for Health and Clinical Excellence; RCT=randomised controlled trial; RT=radiotherapy

Appendix F Additional areas of interest

Articles in this section were identified from the main literature search and targeted, non-systematic searches (see Methods for more detail). A full systematic review on these areas was not conducted therefore the articles identified in this section do not necessarily represent all papers published on these topics.

Investigative procedures in assessing stage to determine management of early-stage cervical cancer

Summary of included papers

Seventeen citations from 15 studies were identified which described the use of investigative procedures either to stage cervical cancer (including stage IB2) or to determine treatment course.[154-170] A number of other papers were identified which focused on the use of these procedures specifically to identify lymph node metastases or parametrial invasion (without mention of staging or treatment decisions) however these are not included here. Three systematic reviews reporting on these factors were identified,[171-173] and a brief narrative summary of the findings from these reviews have been provided as an overview.

Guidelines

In addition, two guidelines were identified regarding staging cervical cancer.[133, 134]

One guideline by the European Society of Urogenital Radiology (ESUR), on staging of cervical cancer with MRI, recommended MRI for staging of tumours stage IB1 and over or smaller tumours, if trachelectomy is being considered.[134]

Another guideline by the American College of Radiology[133] recommended that for FIGO stage IB2, tumour size >4cm, the following pre-treatment imaging is usually appropriate: MRI pelvis without and with contrast, FDG-PET/CT whole body. It is noted that appropriateness can depend on clinical circumstances, availability, and expertise. Imaging which may be appropriate include: MRI pelvis without contrast, X-ray chest, CT abdomen and pelvis with contrast. The following imaging was considered as usually not appropriate: CT abdomen and pelvis without contrast, US pelvis transvaginal, US pelvis abdominal, US abdomen, CT abdomen and pelvis without and with contrast, X-ray contrast enema, X-ray intravenous urography, ^{99m}Tc bone scan whole body.

Quality assessment

The reviews and primary papers were considered of medium to high quality. Most of the prospective studies were conducted with consecutive patients and blinded, however the retrospective studies were often not blinded when comparing diagnostic accuracy of various investigative procedures to stage cervical cancer.

Study characteristics

Study characteristics of the systematic reviews and primary papers are provided in Tables 15 and 16 respectively. Some papers in this section included less than 10% stage IB2 cervical cancer patients in the population.

One study, ACRIN 6651/GOG 183, was reported by three citations: two prospective analyses reporting different outcomes,[159, 160] and one retrospective analysis of a subset of the study.[168]

Table 16 Study characteristics for systematic reviews on investigative procedures to stage cervical cancer

Study	Population	Investigative procedures	Outcomes
Selman 2008[171] Systematic review including 72 studies	Primary cervical cancer IB2: not stated	SNB, PET, MRI, CT	Lymph node status
Fagotti 2007[172] Systematic review including 10 studies	Locally advanced cervical cancer 6.6% IB2-IIA, IB2: not stated	Surgical staging	Intraperitoneal spread, lymph node involvement, survival
Bipat 2003[173] Systematic review including 57 studies	Cervical cancer IB2: not stated	CT or MRI	Parametrial, bladder or rectum invasion, lymph node involvement

CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography; SNB=sentinel node biopsy

Table 17 Study characteristics for primary papers on investigative procedures to stage cervical cancer

Study	Population	Intervention	Control	Outcomes
Epstein 2013[154] Prospective diagnostic study	Early stage cervical cancer (IA2-IIA) N=182 IB2: 13%	US or MRI	Histology	Tumour size, stromal and parametrial invasion
Shweel 2012[155] Prospective study	Cervical cancer N=30 6.6% IB, IB2: not stated	MRI	Histopathology	Staging, parametrial and vaginal infiltration
Dhoot 2012[156] Prospective study	Cervical cancer N=75 29.3% IB, IB2: not stated	MRI or clinical exam	Histopathology for stages ≤IIA; consensus review by experts for >IIA	Staging, impact on treatment decisions
Rajaram 2010[157] Prospective diagnostic study	FIGO stage I and II cervical cancer N=25 IB2: not stated	Clinical exam, CT or MRI	Histopathology/ cytology	Staging, detection of vertical extension

Study	Population	Intervention	Control	Outcomes
Marana 2009[158] Prospective study	FIGO stage IB2-IIIB cervical cancer N=98 IB2: 11%	Surgical staging	Clinical staging	Survival, surgical outcomes, staging
Mitchell 2006[159] Prospective diagnostic study - ACRIN 6651/GOG 183	Early cervical cancer N=172 of 208 65% IB, IB2: not stated	Clinical exam, CT or MRI	Surgicopathologic findings	Detection of tumour size, uterine or cervical stromal involvement
Hricak 2005[160] ACRIN 6651/GOG 183	Early cervical cancer N=172 of 208 IB2: 9.90%	Clinical exam, CT or MRI	Surgicopathologic findings	Determining stage, detection of rectal, bladder or lymph node involvement
Akata 2005[161] Prospective study	Cervical cancer N=28 43% IB, IB2: not stated	MRI	Surgical or pathological staging	Staging, impact on treatment decision
Denschlag 2005[162] Prospective case series	Primary invasive cervical cancer N=59 51% IB, IB2: not stated	Extraperitoneal lymph node dissection		Lymph node involvement, impact on treatment planning
Mastilovic 2011[163] Retrospective review, abstract	Early cervical cancer (stage IB1-IIB) N=294 IB2: 8%	Clinical exam	Histopathology	Staging
Stenstedt 2011[164] Retrospective review	Cervical cancer N=183 IB2: 14%	MRI		Effect of MRI on treatment planning
El-Ghamry 2010[165] Case series, abstract	Cervical cancer N=74 23% IA1-IIA, IB2: not stated	PET/CT		Impact on radiotherapy treatment planning
Qin 2009[166] Retrospective review	Operable cervical cancer (IB-IIB) N=818 IB2: 6%	Clinical exam	Pathology	Staging, vaginal and parametrial invasion
Hancke 2008[167] Retrospective review	Cervical cancer N=255 clinical exam, 164 CT, 101 MRI IB2: 7.5%	Clinical exam, CT or MRI	Surgicopathologic findings	Detection of parametrial involvement, lymph node metastasis, treatment decisions
Hricak 2007[168] Retrospective review – data set: ACRIN 6651/GOG 183	Early cervical cancer N=156 IB2: not stated	CT or MRI	Pathology	Staging, tumour visualisation, evaluation of parametrium

Study	Population	Intervention	Control	Outcomes
Sahdev 2007[169] Retrospective review	Early cervical cancer N=150 10.7% >4cm; IB2: not stated	MRI	Histopathology	Tumour staging, tumour size, detection of lymph node involvement
Ozsarlak 2003[170] Retrospective review	Primary cervical cancer N=36 IB2: 22%	Clinical exam, CT or MRI	Histopathology	Staging, detection of lymph node metastases

CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography; SNB=sentinel node biopsy; US=ultrasound

Outcomes

Systematic reviews

Selman et al (2008)[171] reported that sentinel node biopsy provided a more accurate assessment of lymph node metastasis compared with PET, MRI and CT.

Fagotti et al (2007)[172] described the impact of pre-treatment laparoscopic staging in locally advanced cervical cancer patients. The authors concluded that pre-treatment surgical staging can identify positive nodes in clinically node negative patients, therefore treatment may be tailored.

The systematic review by Bipat et al (2003)[173] found that MRI was more accurate than CT in detecting parametrial invasion and lymph node involvement. The authors noted MRI can play an important role in advanced disease, however the additional value of MRI is limited in clinically early-stage cervical cancer (as prevalence of spread of disease outside the cervix is low).

Survival

One prospective study by Marana et al (2009)[158] reported survival outcomes between patients who were surgically staged and those who were clinically staged. Five-year overall survival for the entire group was 63%, estimated 5-year OS for surgically staged patients was 80.6% and for clinically staged patients was estimated to be 51.1% ($p<0.007$).

Improved accuracy of staging

Studies reported on the accuracy of various methods to stage cervical cancer, as compared with the reference standard, usually histopathology, see Table 17.

Using surgicopathologic staging as a reference standard, MRI was often reported as a more accurate method of staging than CT or clinical examination.[156, 157, 160, 161, 170] One study reported similar rates of accuracy between MRI and CT.[167] One study reported that CT was more accurate than MRI for stage ≤IIA, however MRI was more accurate for stage >IIA.[168]

Some studies reported results of accuracy of imaging by stage. The diagnostic accuracy of clinical exam,[156, 158, 163, 166] MRI[155, 168, 170] and CT[168, 170] was superior for cervical cancers of lower stage. One prospective study reported high rates of accuracy of MRI in higher stages (100% for stage IIIB, IVA and IVB).[156]

Specific to stage IB2, in the large retrospective study by Qin et al (2009),[166] the accuracy of clinical examination for stage IB2 was 77.4%, however a smaller retrospective study[163] (reported in abstract only) reported that clinical exam understaged 54% and overstaged 2% of stage IB2 cervical cancers.

Table 18 Accuracy of investigative procedures to stage cervical cancer

Study	Reference standard	Imaging method	Stage	Accuracy	Understaged	Overstaged
Epstein 2013[154] N=182	Histology	MRI	IA2-IIA	93% agreement		
		US		95% agreement		
Shweel 2012[155] N=30	Histopathologic staging	MRI	All	92.2%		
			IB	100% agreement		
			IIA			1 or 2 cases+
			IIB			1 or 2 cases+
			IVA	100% agreement		
Dhoot 2012[156] N=75	Histopathology for stages ≤IIA; consensus review by experts for >IIA	MRI	All	89.3%		
			IA	0		
			IB	86%		
			IIA	100%		
			IIB	93%		
			IIIA	0		
			IIIB	100%		
			IVA	100%		
			IVB	100%		
		Clinical exam	All	61.3%		
			IA	100%		
			IB	82%		

Study	Reference standard	Imaging method	Stage	Accuracy	Understaged	Overstaged
			IIA	0		
			IIB	75%		
			IIIA	0		
			IIIB	42%		
			IVA	0		
			IVB	0		
Rajaram 2010[157] N=25	Histopathology/ cytology	CT	I & II	52%	20%	28%
		MRI		80%	4%	16%
		Clinical exam		68%	12%	20%
		Clinical exam + CT		80%		
		Clinical exam + MRI		96%		
Marana 2009[158] N=98	Surgical staging	Clinical staging	IB2-IIIB	50% agreement	17%	33%
			IB and IIA	71.4% agreement		
			IIB	47.6% agreement		
			IIIB	28.6% agreement		
Hricak 2005[160] N=172	Surgicopathologic findings	CT	Early	32% agreed exactly		
		MRI		42% agreed exactly		
Akata 2005[161] N=28	Surgical findings	MRI	IA2-IIA	82%		
		Clinical exam		57%	39%	4%
Mastilovic 2011[163] N=294	Histopathology	Clinical exam	IB1-IIB		21%	19%
			IB1		10%	20%
			IB2		54%	2%
			IIA		70%	30%
			IIB		35%	7%

Study	Reference standard	Imaging method	Stage	Accuracy	Understaged	Overstaged
Qin 2009[166] N=818	Pathological classification	Clinical exam	IB-IIB	53.1%	9.7%	37.3%
			IB1	85.4%		
			IB2	77.4%		
			IIA	35.3%		
			IIB	20.5%		
Hancke 2008[167] CT n=164 MRI n=101	Surgicopathologic findings	CT	≤IIA*	54%		
			≥IIB*	61%		
		MRI	≤IIA*	56%		
			≥IIB*	61%		
Hricak 2007[168] N=156	Pathology	CT	≤IIA	82.7-100%		
			>IIA	13-37%		
		MRI	≤IIA	75.2-79.5%		
			>IIA	40-57%		
Ozsarlak 2003[170] N=36	Histopathology	CT	All stages	53%	31% (of which 80% had treatment implications)	9% (with treatment implications)
			IB	86%		
		MRI	All stages	86%	7% (with treatment implications)	0
			IB	100%		
		Clinical exam	All stages	47%	44% (of which 87% had treatment implications)	8% (with treatment implications)
			IB	100%		

[+] unclear in text; *palpation-staged. CT=computed tomography; MRI=magnetic resonance imaging; US=ultrasound

Treatment planning

A limited number of papers were identified which explicitly stated differences in treatment decisions based on the results of various imaging procedures.

Dhoot et al (2012)[156] reported that MRI detected significant additional findings than clinical examination in 23 (out of 75) patients. The treatment strategy was significantly altered in 20 of these patients (26.6% of total study population). Thirteen per cent were treated with surgery rather than primary radiotherapy, 26% received primary radiotherapy instead of surgery. Forty-five per cent of the patients whose treatment was altered were upstaged to stage IV following MRI findings.

Stenstedt et al (2011)[164] reported that in 10 of 125 surgery cases (8%), medical records indicated that MRI results affected treatment planning (in the remaining cases, the impact of MRI on treatment planning could not be determined). In three of seven cases undergoing trachelectomy, MRI was used to help the surgeon in the decision. In 20.7% of radiotherapy cases MRI results affected treatment planning and was noted to be particularly useful in two obese patients.

The abstract reported by El-Ghamry et al (2010)[165] indicated that the radiation fields were modified based on PET/CT findings in 36.5% of patients (7% in early stage, including IB, patients; 93% in advanced stage).

In contrast, the study reported by Hancke et al (2008)[167] concluded that imaging by CT or MRI was not reliable enough to change treatment decisions that had been made clinically by palpation.

Denschlag et al (2005)[162] reported that following results of surgical staging, treatment was modified in 27% of patients.

Summary

Three systematic reviews and 15 diagnostic studies were identified on different pre-treatment investigative procedures used for cervical cancer patients. MRI appeared to be more accurate for staging cervical cancer than PET/CT or clinical examination. Some studies concluded that additional procedures were of most use for more advanced cervical cancer. Investigative procedures such as MRI and PET appear to have benefit in treatment decisions, however this was mainly observed with advanced cancer patients.

Influence of length of time to treatment on outcomes for women with stage IB2 cervical cancer

Summary of included papers

Two relevant studies were identified which investigated the influence of length of time to treatment on outcomes for women with stage IB2 cervical cancer. Both studies were

retrospective reviews of case records, one reported on the waiting time for surgery,[174] the other for radiotherapy.[175]

Quality assessment

Formal quality assessment was not performed for case series as they are considered a lower quality of evidence than comparative studies.

Study characteristics

Study characteristics of the time-to-treatment studies are in Table 18.

Table 19 Characteristics of time-to-treatment studies

Study	Population	Time factors examined	Outcomes
Umezu 2012[174] Retrospective case series	Stage IA-IIA cervical cancer treated surgically N=117 IB2: 13.6%	Waiting time to operation - <50 days vs >50 days	OS, RFS
Choan 2005[175] Retrospective case series	Cervical cancer patients treated with RT N=195 25% stage IB; IB2: not stated	Delays in treatment (radiotherapy) initiation - From consult - From examination - From diagnosis	OS, DFS, progression

DFS=disease-free survival; OS=overall survival; RFS=relapse-free survival; RT=radiotherapy

Outcomes

Survival

The study by Umezu et al (2012) found that waiting time to surgery did not influence overall or relapse-free survival.[174] Five-year overall survival was 96.7% for those waiting less than 50 days for surgery and 92.5% for those waiting more than 50 days (p=0.653). Five-year relapse-free survival was 91.4% for those waiting less than 50 days for surgery and 80.9% for those waiting more than 50 days (p=0.106).

The study by Choan et al (2005) found that radiotherapy waiting time alone was not significantly associated with survival, however when assessed as part of a multivariate analysis, prolonged waiting times did have a negative impact on overall and disease-specific survival, but not disease progression.[175] This effect was seen for all delays: between consult and radiotherapy, between examination under anaesthesia to radiotherapy and diagnosis to radiotherapy. However, the analysis did not produce a cut-off interval beyond which the survival outcome was adversely affected.

Adverse events/toxicity

Adverse events were not reported in the included studies.

Quality of life/psychosocial outcomes

Quality of life and/or psychosocial outcomes were not reported in the included studies.

Summary

Only two studies, both case series, were identified regarding the influence of time to treatment on outcomes for patients with stage IB2 cervical cancer. One study reported no survival impact regarding waiting time for surgery. The other reported longer waiting times for radiotherapy may adversely impact survival. Adverse events and quality of life data were not reported.

Abbreviations

AA	Additional area
ACR	American College of Radiology
ART	Abdominal radical trachelectomy
ASCO	American Society of Clinical Oncology
BMI	Body mass index
BRT	Brachyradiotherapy
BT	Brachytherapy
CCO	Cancer Care Ontario
CCT	Controlled clinical trial
CI	Confidence interval
CPG	Clinical practice guideline
CR	Complete response
CRT	Chemoradiotherapy
CSS	Cause-specific survival
CT	Computed tomography
DFI	Disease-free interval
DFS	Disease-free survival
EFS	Event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society of Medical Oncology
ESUR	European Society of Urogenital Radiology
FACT-B	Functional Assessment of Cancer Therapy - Breast
FDG	Fludeoxyglucose
FIGO	Féderation Internationale de Gynécologie et d'Obstétrique
GIN	Guidelines International Network
HR	Hazard ratio
ICSI	Intracytoplasmic sperm injection
IGCS	International Gynecologic Cancer Society
IMRT	Intensity modulated radiotherapy
INA	Information not available
IP	Ifosfamide/cisplatin
IUI	Intrauterine insemination
IVF	In vitro fertilisation
JCOG	Japan Clinical Oncology Group
LARVH	Laparoscopically-assisted radical vaginal hysterectomy

LND	Lymph node dissection
M/C	Multicentre
MFS	Metastasis-free survival
MRI	Magnetic resonance imaging
N/A	Not applicable
NACRT	Neoadjuvant chemoradiotherapy
NACT	Neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NGC	National Guidelines Clearinghouse
NICE	National Institute for Health and Clinical Excellence
NR	Not reported
NS	Not significant
OR	Odds ratio
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PR	Partial response
QoL	Quality of life
RCT	Randomised controlled trial
RFS	Relapse-free survival
RH	Radical hysterectomy
RQ	Research question
RR	Relative risk
RT	Radiotherapy
S/C	Single centre
SCC	Squamous cell carcinoma
SIGN	Scottish Intercollegiate Guidelines Network
SNAP	Studio Neo-Adjuvante Portio
SNB	Sentinel node biopsy
SS	Statistically significant
TIP	Paclitaxel/ifosfamide/cisplatin
TP	Paclitaxel/cisplatin
US	Ultrasound
VRT	Vaginal radical trachelectomy
WHO	World Health Organisation

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