Full Title: Variation in Outcome Reporting in Studies of Fertility-Sparing Surgery for Cervical Cancer: a Systematic Review

Running Title: Outcomes for Fertility-Sparing Surgery for Cervical Cancer

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Abstract

Background: Cervical cancer affects 3,197 women in the UK, and 604000 women worldwide annually, with peak incidence seen between 30-34 years of age. For many, fertility-sparing surgery is an appealing option where possible. However, absence of large-scale data, along with a notable variation in reported outcomes in relevant studies may undermine future efforts for consistent evidence synthesis.

Objectives: To systematically review the reported outcomes measured in studies that include women who underwent fertility-sparing surgery for cervical cancer and identify whether variation exists.

Search Strategy: We searched MEDLINE, EMBASE, and CENTRAL from inception to February 2019.

Selection Criteria: Randomised controlled trials, cohort and observational studies, and case studies of more than 10 participants from January 1990 to date.

Data Collection and Analysis: Study characteristics and all reported treatment outcomes.

Main results: 104 studies with a sum of 9535 participants were identified. Most studies reported on oncological outcomes (97/104), followed by fertility and pregnancy (86/104), post-operative complications (74/104), intra-operative complications (72/104), and quality of life (5). There were huge variation and heterogeneity in reported outcomes, with only 12% being good quality and 87% being of poor quality.

Conclusions: There is significant heterogeneity in the reported outcomes. An agreed Core Outcome Set (COS) is necessary for future studies to effectively

harmonise reported outcomes that are measurable and relevant to patients, clinicians, and researchers. This systematic review sets the groundwork for the development of a COS for fertility-sparing surgery in cervical cancer.

Funding: British Medical Association's Strutt and Harper Grant.

Keywords: cervical cancer; fertility-sparing; core outcomes

Tweetable Summary: Many women with cervical cancer wish to use surgery that preserves fertility. There is a lot of variation in how studies are reported making it difficult to draw firm conclusions. A Core Outcome Set is essential to improve the quality of clinical study reporting.

Introduction

Cervical cancer is the 4th most common cancer in women, with a global incidence of 13.1 per 100,000 women annually(1). The incidence of cervical cancer peaks at 30 - 34 years, when many women may not have completed their families (1). Cervical cancer staging involves clinical examination, colposcopy, histological assessment and radiological imaging (MRI (local extent), CT (distant disease))(2-4), and is based on the International-Federation of Obstetrics-&-Gynaecology (FIGO) 2018 revised classification (5-7).

Generally, early stage (IA1) cervical cancer treatment can be in the form of large loop excision of transformation zone (LLETZ) or cone biopsy. The presence of lymphovascular space invasion (LVSI) or stage IA2 disease may necessitate pelvic lymph-node dissection to prevent under-staging and assess need for adjuvant treatment. Radical hysterectomy with pelvic lymphadenectomy has been the gold standard management for stage IA2 (LVSI) to IB1 disease(8, 9). As a principle, stage IA1 through IB1 disease is amenable to surgery subject to individual assessment, although some IB1 cases may be equally or preferably managed with radiation therapy. Stage IB2 and above is usually treated with cisplatin based chemoradiation(10-14).

The age distribution of cervical cancer- implies that a proportion of women may yet to complete their family. Regardless, loss of fertility can cause psychological distress and impacts women's quality-of-life (15-17). Several fertility-sparing surgical options have been introduced to address this. These include radical trachelectomy (vaginal,

112 open abdominal, laparoscopic, robotic approaches) with pelvic lymph node
113 assessment. It also includes local treatments in the form of LLETZ, conisation, or
114 simple trachelectomy. Key cornerstone criteria to proceed with fertility-sparing
115 surgery the desire for, or the likelihood of fertility, and oncological safety (15).

116

117 *Reported Outcomes after a Fertility-Sparing Approach*

118 FIGO recommends that women diagnosed with cervical cancer FIGO stage 1A1 –
119 1B1 can be offered a fertility-sparing treatment if they wish to conceive (18).
120 Although these fertility-sparing surgical alternatives have been in practice for over
121 three decades, questions remain regarding oncological safety, their efficacy and
122 outcomes, and the superiority of one procedure over another(15, 19-22). To address
123 this issue, clinicians require robust data from high-quality systematic reviews and/or
124 large-scale prospective studies. A move forward towards this direction would need
125 global consensus on achieving homogenously reported outcomes in such studies.
126 For example, several original studies report a melange of outcomes tailored to
127 measure cancer survival, surgical morbidity, sexual function post treatment,
128 pregnancy success rates, and other vital outcomes(23-27). However, the variation in
129 reporting quality and outcome measures across studies impairs evidence synthesis
130 and poses a hindrance to robust evidence-based developments in the field.

131

132 This challenge has been recognised in other fields of our specialty. To address this,
133 several journal editors together set the foundation for “CoRe Outcomes in Women’s
134 and Newborn health” (CROWN) initiative(28). CROWN initiative aims to produce,
135 disseminate, and implement core outcome sets (COS) which is a stepping stone to

advance research quality and usefulness(29). It also sets the ground for homogenisation of reported outcomes to facilitate evidence synthesis and accommodate the vision of delivering robust evidence. This can form the basis of guidelines and policies to improve decision making and evidence-based practice(29). By the term COS, we refer to a minimum collection of outcomes with standardised measurement and reporting, which are prioritised by stakeholders, researchers, and clinicians(29-31).

To date, there is no reported COS for studies that discuss fertility-sparing surgery for women diagnosed with cervical cancer. To this end, we performed a systematic review to identify and characterise the variation of reported outcomes in studies investigating fertility-sparing surgery for cervical cancer. This systematic review aims to form the groundwork for the development of the relevant COS.

Methods

We followed a prospectively designed protocol with distinct study selection criteria. The objectives of this systematic review (SR) fell outside the PROSPERO registry criteria(30, 32). This SR was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA, supplementary information).

Study eligibility

We included all published randomised control trials, cohort studies, observational studies, and case series with a minimum of 10 participants. All participants involved had some form of fertility-sparing surgery (for example, trachelectomy, conisation, excision) for a confirmed histological diagnosis of adenocarcinoma, squamous cell carcinoma, or adeno-squamous carcinoma of the cervix. Studies that involved pregnant women were also included in the analysis.

Study types excluded were case reports, histological diagnoses not previously listed such as clear cell carcinoma or neuroendocrine neoplasms, studies primarily aimed at assessing pharmacokinetics, mechanism of drugs, technical results of novel devices, radio-imaging or histological or physiological data. We used a pragmatic date cut-off to capture all studies based on modern practice and excluded studies prior to 1990.

Systematic review publications were included during the literature review to cross-reference and identify studies not captured during the initial literature search. Studies reported in conferences or when only an abstract was available were excluded from the final review.

Search strategy

A systematic literature review was undertaken by searching MEDLINE, EMBASE, and CENTRAL until the 27th of February 2019 (33, 34). Search terms included “cervical cancer”, “tumour”, “neoplasm”, “malignancy”, “large loop excision of

transformation zone", "lletz", "leep", "cone", "conisation", "cervicectomy", "trachelectomy", "surgery", "biopsy", "fertility", and "fertility sparing". There was no language restriction applied to the literature search. Appendix S1 describes our search strategy.

Data extraction

Two reviewers (NY and CB) independently assessed the titles and abstracts using predefined study eligibility criteria described above. Full articles were then obtained, and data on all reported outcomes were extracted using an agreed pre-specified extraction sheet. Discrepancies were resolved by discussion and input of a third party if necessary. Descriptive statistics were used to map the characteristics of reported COS. Data were presented in comprehensive tables.

Quality assessment

JADAD scoring was used for assessing the methodological quality of randomised controlled trials (RCT)(35). Any study which scored ≥3 (maximum score= 5) was considered medium to high quality. Quality of reporting of outcomes in RCTs was assessed using the 6-point Management of Otitis Media with Effusion in Cleft Palate (MOMENT) criteria(36). A trial that scores ≥4 (maximum score= 6) is considered high quality.

The quality of non-randomised studies was scrutinised using the Newcastle Ottawa Scale (NOS)(37).

Patient involvement

There was no direct patient involvement in this systematic review.

Core outcomes

There are no previously stated core outcomes within our field of study. Therefore, this systematic review will form part of the process in developing a set of core outcomes for women diagnosed with cervical cancer and undergoing fertility-sparing surgery as part of the Core Outcome sets for Gynaecological conditions (COGS) project.

Funding

This study is funded by the British Medical Association's Strutt and Harper Grant. The funders have no involvement in any stage of this systematic review.

Results

The literature search yielded a total of 937 studies, of which 355 duplicates were removed; 582 titles were screened against our inclusion criteria, and 452 abstracts were fully assessed. Of those abstracts, 130 full texts were scrutinised, and 51 failed to meet the inclusion criteria, leaving 79 studies for inclusion in our analysis(25, 38-115). Additionally, the literature search yielded several systematic reviews, which

were manually assessed, and we further identified 25 studies not captured by the initial literature search(26, 116-139).

In total, 104 studies were included for the final analysis, with a cumulative sum of 9535 participants. Figure 1 summarises the study selection process (PRISMA flowsheet).

Study characteristics

We included 22 cohort studies, 32 prospective observational studies, 57 retrospective observational studies, and 4 case series. There was no published randomised controlled trial that met our inclusion criteria. The population of included studies were from North America, Europe, and Asia, with only two representing South America and one from the Middle East. There was one international collaborative study that took place in the United States, Columbia, and Brazil, and 11 multi-centre studies.

Of the cohort studies, 11/22(50%) compared fertility-sparing interventions against hysterectomy. The remainders compared two different fertility-sparing procedures. 12/104 studies (12%) included patients who received neoadjuvant chemotherapy before surgery(25, 26, 62, 76, 82, 85, 86, 125, 128, 129, 135, 140). Nine studies (9%) described patients who underwent sentinel lymph node mapping as part of the surgical workup(62, 64, 65, 69, 80, 85, 102, 109, 116). The full characteristics of the included studies are summarised in Table S1.

97 studies included participants with FIGO stage IA1 - IB1 cervical cancer. There were seven studies with patients with stage IIA disease and two studies with stage IIB disease. Seven studies did not specify the stage of the disease. 65 studies did not specify primary outcomes. Of those which had set primary outcomes, only one included secondary outcomes in its reporting.

Vaginal trachelectomy was the most common form of fertility-sparing surgery reported with 63 out of 104 trials (61%), followed by open abdominal trachelectomy with 32 (31%) trials. A comprehensive breakdown is detailed in Table S2.

Outcomes

This review has drawn five broad categories of outcomes: (i) intra-operative, (ii) post-operative, (iii) fertility and pregnancy, (iv) oncological, and (v) quality-of-life (QoL) outcomes. 72 (69%) reported intra-operative outcomes. 74 (71%) reported post-operative outcomes. 86 (83%) reported outcomes relating to fertility and pregnancy following surgery. 97 (93%) reported oncological outcomes. Five (5%) studies included outcomes related to the quality-of-life following fertility-sparing treatment. Outcomes that did not fit into the categories previously mentioned included those focussed on neonatal outcomes and those related to neoadjuvant chemotherapy. Table 1 outlines a summary of intra-operative, post-operative, quality of life, and miscellaneous outcomes; while Table 2 highlights a summary of fertility and pregnancy outcomes, and oncological outcomes.

Intra-operative outcomes

Of the intra-operative outcomes reported, the commonest variables recorded were blood loss (49/72, 68%), complications (45/72, 63%), duration of the procedure (55/72, 76%), peri-operative blood transfusion (38/72, 53%), and conversion to hysterectomy (31/72, 43%). Most documentation of blood loss did not specify a measurement tool; however, estimated blood loss was the most standard way to record blood loss (14/49, 29%). Other methods included ‘amount recorded from the suction tube’ and ‘the difference in haemoglobin before and after surgery’. 23 (51%) trials that recorded intra-operative complications did not specify the type of complication. Of the complications listed, vascular injury (28/46, 61%) was most common, followed closely by urological issues (26, 57%). Nine studies reported the number of cases that were initially performed with minimally invasive techniques but were converted to laparotomy. 31(43%) of the 72 studies reported the need to convert to a radical hysterectomy. A comprehensive breakdown of all intra-operative outcomes is detailed in Table S3.1.

Post-operative outcomes

Commonly recorded post-operative variables included early and late complications (67/74, 91%), length of stay in hospital (38/74, 51%), time taken for the return of bladder function (12/74, 16%), and duration required for return of menses (13/74, 18%). Other outcomes recorded include duration of need for regular analgesia (1/74, 1%), readmission to hospital (3/74, 4%), and interval from surgery to passing flatus (2/74, 3%). Of the complications recorded, the commonest were either gynaecological or lymphatic in nature. 42 trials (57%) recorded patients with cervical

stenosis/ haematometra requiring dilatation. Menstrual disorder (12, 18%), abnormal bleeding (5, 7%), and amenorrhoea (12, 18%) were also common complaints following surgery. 30 studies (41%) reported the incidence of lymphocysts requiring drainage. 15 (45%) trials documented cases of lower limb oedema/ lymphoedema, and 15 (45%) trials reported women who returned to theatre during the peri-operative period. The number of women requiring emergency hysterectomy in the post-operative period was reported by 3 studies. Urological issues were also recorded, with 10 (14%) studies reporting bladder hypotonia or dysfunction following fertility-sparing surgery, five (7%) recording urinary retention following treatment, and two (3%) cited long term bladder dysfunction. Four studies (5%) reported paralytic ileus and three (4%) noted either partial or complete bowel obstruction following surgery. A comprehensive breakdown of all post-operative outcomes is detailed in Table S3.2.

Fertility and pregnancy outcomes

Fertility and pregnancy outcomes were typical findings in this review, with 47 papers (55%) specifying the inclusion of participants attempting to conceive, and 55 papers (64%) noting women who successfully conceived without fertility intervention. Other reported outcomes were incidence of miscarriage (60/86, 70%) and termination (21/86, 24%), live birth (30/86, 35%), mode of delivery (41/86, 48%), and gestational age at birth (29/86, 34%). Obstetric complications were also reported, with preterm pre-labour rupture of membranes (29/86, 34%) and chorioamnionitis (14/86, 16%) the most common. A comprehensive breakdown of all fertility and pregnancy outcomes is detailed in Table S3.3.

Oncological outcomes

Of the 97 studies which recorded oncological outcomes, the commonest variables were survival (any form of survival outcome 39/97, 40%), recurrence (69, 71%), utilisation of adjuvant therapy (49, 51%), lymph node status (39, 40%), LVSI status (38, 39%), and specimen margin status (32, 33%). Survival outcomes were reported in a variety of ways, including ‘disease-related death’ (23/39, 59%), ‘overall survival’ (4, 10%), ‘disease-free status’ (3, 8%), and ‘5-year recurrence-free survival rate’ (3, 8%). The number of lymph nodes resected was recorded in 38 studies (39%). 64 studies (66%) published data relating to recurrence during the follow-up period, with 33 studies (52%) specifying the site of recurrence as well as the type of treatment provided. Ten studies (10%) highlighted the interval between the initial surgical therapy and confirmation of recurrence of the disease. Several publications (27, 28%) reported the number of women having a hysterectomy within the study follow-up period. Seven of the 97 studies (7%) recorded cytology findings, with two (2%) also highlighting the HPV status during the follow-up period. A comprehensive breakdown of all oncological outcomes is detailed in Table S3.4.

Quality of life outcomes

Quality of life data was less studied, with functional assessment (1/5, 20%) (50), symptom scales (2/5, 40%), and concerns (2/5, 40%) being themes frequently investigated. A comprehensive breakdown of all outcomes relating to quality of life is detailed in Table S3.5.

Other outcomes

Miscellaneous data which did not apply to those mentioned earlier included those related to neoadjuvant chemotherapy (7/12, 58%) and non-disease related surgeries (1/12, 8%).

Of the studies reporting neonatal outcomes, five reported neonatal deaths, four recorded birth weight, and three on neonatal ward admission. As this review included studies that conducted neoadjuvant chemotherapy prior to surgery, complications arising from chemotherapy toxicity and response to chemotherapy were also documented. All miscellaneous outcomes are detailed in Table S3.6.

Outcome measurement

Few studies documented the tools utilised to measure the reported outcomes. Standard measurement tools were those used for documenting survival and mortality rates, such as 5-year overall survival (4) and 5-year recurrence-free survival rates (3). Three studies referenced the Clavien-Dindo classification system when grading complications. One study applied Bailey's scale of infant development to assessment childhood development (21), and different quality of life questionnaires were used in various studies, including QLQ-C30 (1)(50), QLQ-CX24 (1)(50), and FACT (1)(68). A variety of clinical and radiological assessments were used to survey remission during follow-up, including PAP testing (2), annual MRI-pelvis (1), internal examination (1), and colposcopic assessment (1). The different types of measurement tools used are recorded in Table S4.

As there were no randomised control trials in this review, the Newcastle Ottawa Scale (NOS) was applied to assess the quality of the studies in the systematic review. Of which, 13 (12%) were judged as good quality, one (1%) was deemed of fair quality, and 91 (87%) were of poor quality. The breakdown of the NOS assessment can be found in Table S5. Table S6 is included detailing all abbreviations used in this paper.

Discussion

Main Findings

Our systematic review shows international interest in assessing the outcomes of women who undergo fertility-sparing surgery for cervical cancer. Oncological outcomes were the most commonly reported topic in most studies, followed by fertility outcomes. Over half of the studies did not specify primary and secondary outcomes. However, this can be explained by there being no randomised controlled trials eligible for this review. Our data highlight wide heterogeneity in outcomes, limited standardisation in outcome measures, and the existing small proportion of good quality studies. There was heterogeneity in assessing outcomes such as pregnancy losses, survival rate, blood loss, infections, and more. Definitions for outcomes were often either lacking or varied, such as preterm delivery, first or second trimester miscarriage, post-operative infection. This makes drawing

comparisons between studies challenging. Many of the studies included within this systematic review described a broad range of outcomes, while a small proportion of studies set to study more specific outcomes relating to fertility-sparing surgery following a cervical cancer diagnosis; these studies predominantly focussed on quality-of-life impacts or neonatal effects. The deficiency of the methodology used to describe the reported outcomes is also a concern.

Strength and Limitations

This is the first systematic review which seeks to report all relevant outcomes reported in the literature for studies assessing fertility-sparing surgery for cervical carcinoma. A robust methodology was used throughout this review. Imposing no language restrictions allowed us to capture a diverse group of participants to inform this review with 12 studies published in non-English journals. The major limiting factor for this review was that most studies were observational studies, of which only 12% were deemed to be of good quality. We acknowledge that 24% of the studies recorded within this review did not appear during our literature search but were included from other systematic reviews. However, due to the ‘saturation’ of outcomes reported, we can be confident that we are unlikely to have missed any other significant outcomes.

Interpretation

Outcomes described in this systematic review mainly represent the outcomes that several researchers and clinicians have chosen to investigate and report globally. This has been the norm with other systematic reviews that aimed to describe outcomes for benign gynaecological conditions(141). As a result, most studies report predominantly on oncological or fertility-related outcomes. Nevertheless, despite the presence of a dominating theme of outcomes reported, the majority of studies report on a wide range of outcomes with an overall significant variation in reported outcome measures. This is not surprising as several other systematic reviews in other areas of gynaecology report the same findings(142-145). This poses a significant burden when interpreting study findings, essentially limiting those studies' international amplitude and clinical applicability.

More importantly, forming policies, implementing robust guidelines, and describing gold standard practice is predominantly based on the ability of researchers and clinicians to synthesise available evidence effectively. Delivering high-quality systematic reviews and data synthesis can only be possible if reported outcomes are harmonised(146). Additionally, one can argue that initiation of large-scale high-quality trials may be based on robust systematic reviews which successfully demonstrate a need for further research. In our case, variation of reported outcomes directly prohibits robust evidence synthesis and perhaps creates an unfavourable ground to design or undertake a high-quality RCT or well-designed studies targeted to provide answers for knowledge gaps that arise from current studies. Undoubtedly, the observed lack of RCTs can be secondary to ethical challenges; however, lack of available high-quality evidence may lead to a vicious cycle.

From the public and patient's perspective, a patient can only make a properly informed decision if clinicians and researchers are able to provide strong evidence confidently. Lack of harmonised outcomes results in knowledge gaps which would essentially pose a significant burden in standardising evidence-based clinical practice. Subsequently, clinicians may at times be less confident to offer fertility-sparing surgery, and patients may feel nervous about opting for a fertility-sparing option when this perhaps is available and safe; or a corollary may be deciding to opt for fertility-sparing surgery which is ill-informed and in retrospect may be regretted. Further to this, our primary search failed to demonstrate patient-centred outcomes, and QoL was only reported in only 5 studies. Thus many of the outcomes most frequently reported are those that are easy to collect and not very meaningful to patients. This emphasises the need for active patient and public involvement (PPI) in developing COS. Fertility-sparing treatment must be offered on the basis of patients' wishes. Any effort to develop and identify COS should incorporate patients' in the process and represent their views as one of the important components. We speculate that a final COS is likely to include outcomes like overall survival, progression free survival, cancer specific mortality, recurrence, surgical complications, live birth rate, fetal loss, quality of life, and patient satisfaction amongst others.

Overall, this underlines the necessity of agreeing to design, disseminate, and implement COS for fertility-sparing surgery in cervical cancer. This will facilitate an international consensus in reporting outcomes following fertility-sparing interventions,

and therefore allow interpretation of each study on a global scale. It will also act as a catalyst to bring experts and stakeholders from international institutions, societies, and patient groups together, to agree on establishing robust guidelines as to when fertility-sparing surgery is indicated, its oncological safety profile, contraindications, surgical morbidity, potential impact, effect on QOL, as well as success in pregnancy related outcomes post treatment. Well-established evidence-based guidelines make clinicians confident to counsel women effectively and to utilise the option of fertility-sparing surgery wisely when this is indicated, as well as helping patients make informed decisions on whether to opt for the intervention.

Conclusion

We recommend the development COS for fertility-sparing surgery in cervical cancer. This will prevent unnecessary duplication of research time and provide key stakeholders including patients, clinicians, nurses, researchers and allied health professionals as well as professional societies, with the opportunity to identify outcome sets prospectively whilst designing their study. This can also facilitate ethics committee's approval of novel trial protocols as it provides a form of standardised approach (30, 147). Delivering COS will facilitate a global approach towards providing high-quality evidence in the field of fertility-sparing surgery for cervical cancer.

Our data highlights heterogeneity in the reporting of outcomes used in studies of fertility-sparing surgery for cervical carcinoma. A defined set of agreed core outcomes is critical to facilitate future studies, for research studies to be meaningfully

compared to advise clinical practice and drive forward management change and informed decision making. The decision to proceed with fertility-sparing surgery is predominantly patient-centred. It is essential that patients and public stakeholders be involved in the development of COS and the final COS also reflect outcomes that are important to them. This systematic review will inform the development of a core outcome set by forming the basis of a broad based Delphi survey, with the addition of data from qualitative work with patients.

Table list

Table 1: Reported intra-operative, post-operative and quality of life outcomes

Table 2: Reported fertility and oncological outcomes

Figure List

Figure 1: PRISMA flowchart

Supplementary Material list

Supplementary information: PRISMA checklist

Appendix S1: Search Strategy

Table S1: Included Studies' characteristics

Table S2: Fertility-sparing surgical procedures and their frequencies described

Table S3.1: Intra-operative Outcomes Reported (Comprehensive)

Table S3.2: Post-operative Outcomes Reported (Comprehensive)

Table S3.3: Fertility and Reproductive Outcomes (Comprehensive)

Disclosure of Interests

NAMC, KSK, and RM have received grant funding from Cancer Research UK (CRUK) to develop core outcome sets for endometrial cancer and atypical endometrial hyperplasia. NC has received a starter grant from the Academy of Medical Sciences to develop a core outcome set for heavy menstrual bleeding. The remaining authors have no competing interest to disclose.

Contribution of Authorship

NAMC and KSK developed the methodology, secured funding, and ethical approval. RM refined the protocol. NY and CB performed the systematic search, and NY wrote the initial draft of the paper. RM, MS, MI refined and finalised the manuscript. AT, MS, and RM provided insight regarding cervical cancer and staging. All authors edited and accepted the manuscript prior to submission.

Details of Ethics Approval

Although ethical approval is not required for a systematic review, the core outcome set project needed ethical approval for the second part of the process which involves patients. Therefore, the project as a whole was reviewed, and East Midlands granted ethical approval - Nottingham 1 Research Ethics Committee on 14th December 2015, REC reference ID 15/EM/0565.

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