Full Title: Variation in Outcome Reporting Identified 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: A Core Outcome Set is needed to improve the quality of clinical study reporting for women with cervical cancer who wish to preserve fertility.

Introduction

Cervical cancer is the 4th most commonly diagnosed neoplastic disease in women, with a global incidence of 13.1 in 100,000 women a year(1). Unlike other common cancers, the incidence of cervical cancer peaks at the age of 30 - 34 years, when many women may have not completed their families yet(1). Current staging of cervical cancer is based on clinical examination, colposcopy assessment of Transformation Zone (TZ), histological assessment, and the use of imaging, mainly in the form of magnetic resonance imaging or ultrasound (for local extension) and computer tomography (with or without positron emission tomography) to exclude distant disease(2-4) including nodal assessment. The British Society of Gynaecological pathologists has currently adopted the International Federation of Obstetrics and Gynaecology (FIGO) 2018 revised classification for the staging of cervical cancer, ranging from stage IA1 to IVB(5, 6).

In general, 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) in the specimen or stage IA2 disease may necessitate further pelvic lymph node dissection to prevent under-staging and the need for adjuvant treatment. Despite some debate over the last century, radical hysterectomy with pelvic lymphadenectomy has been the gold standard treatment for stage IA1 (LVSI) to IB1 disease(7). The term “radical” refers to the removal of greater parametrial and vaginal tissue to achieve additional margins. 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 mostly approached with cisplatin based chemoradiation(8-12).

Cervical cancer's demographic age distribution implies that a significant proportion of women may yet to complete their family. Regardless, loss of fertility can cause psychological distress and drastically impact women's quality of life (13-15). Several fertility sparing surgical options have been introduced to address this. These include a range of radical approaches, i.e., radical trachelectomy in the form of vaginal, open abdominal, laparoscopic, robotic or vaginal approach with pelvic lymph node assessment (lymphadenectomy or sentinel node excision). It also includes local treatment in the form of LLETZ, conisation, or simple trachelectomy. The main dilemma posed by such approaches is whether oncological outcomes are as safe as with conventional radical approaches. Hence the cornerstone criteria to proceed with fertility sparing surgery are the strong desire for, or the likelihood of fertility and oncological safety (13).

Reported Outcomes after a Fertility Sparing Approach

Currently, FIGO recommends that women diagnosed with cervical cancer FIGO stage 1A1 - 1B1 can be offered a fertility sparing treatment if they wish to conceive in the future (16). This is predominantly recommended in small volume tumours, i.e., ≤2cm in size. Advances in surgical technology have allowed the development of tissue-sparing, minimally invasive approaches with subsequent improvement of cancer survival and potentially overall quality of life post treatment. Although these surgical fertility-sparing alternatives have been in practice for over three decades,

there are still questions regarding their efficacy and outcomes and the superiority of one procedure over another(17-20). To address this issue, clinicians require robust data from high-quality systematic reviews or large-scale prospective studies. A move forward towards this direction would be a global consensus on achieving homogenously reported outcomes in such studies. For example, several original studies report a melange of outcomes tailored to measure cancer survival, surgical morbidity, sexual function post treatment, pregnancy success rates, and other vital outcomes(21-25). However, the variation in reporting quality and outcome measures across studies impairs evidence synthesis and poses a hindrance to robust evidence-based developments in the field.

The same challenge has been recognised in other fields of our specialty. To address this, several journal editors came together and set the foundation for an ambitious project under the name “CoRe Outcomes in Women’s and Newborn health” (CROWN) initiative(26). CROWN initiative aims to produce, disseminate, and implement core outcome sets (COS) which essentially will be a stepping stone to advance research quality and usefulness(27). It also sets the ground for homogenisation of reported outcomes which would facilitate evidence synthesis and accommodate the vision of delivering robust evidence; this will be the basis of guidelines and policies to improve decision making and evidence-based practice(27). 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(27-29).

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(28, 30). 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, and studies which included participants who had surgery before the year 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 (31, 32). 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.

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)(33). 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(34). 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)(35).

Patient involvement

There was no 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(23, 36-113). 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(24, 114-137).

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 were cohort studies, 32 prospective observational studies, 57 retrospective observational studies, and 4 were 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(23, 24, 60, 74, 80, 83, 84, 123, 126, 127, 133, 138). Nine studies (9%) described patients who underwent sentinel lymph node mapping as part of the surgical workup(60, 62, 63, 67, 78, 83, 100, 107, 114). 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 studies (69%) reported intra-operative outcomes. 74 studies (71%) reported post-operative outcomes. 86 studies (83%) reported outcomes relating to fertility and pregnancy following surgery. 97 studies (93%) reported oncological outcomes. Five studies (5%) included outcomes related to the quality of life following fertility-sparing treatment. Outcomes that did not fit into the aforementioned categories 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 (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

342 the site of recurrence as well as the type of treatment provided. Ten studies (10%)
343 highlighted the interval between the initial surgical therapy and confirmation of
344 recurrence of the disease. Several publications (27, 28%) reported the number of
345 women having a hysterectomy within the study follow-up period. Seven of the 97
346 studies (7%) recorded cytology findings, with two (2%) also highlighting the HPV
347 status during the follow-up period. A comprehensive breakdown of all oncological
348 outcomes is detailed in Table S3.4.

349

350 *Quality of life outcomes*

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

355

356 *Other outcomes*

357 Miscellaneous data which did not apply to those mentioned earlier included those
358 related to neoadjuvant chemotherapy (7/12, 58%) and non-disease related surgeries
359 (1/12, 8%).

360

361 Of the studies reporting neonatal outcomes, five reported neonatal deaths, four
362 recorded birth weight, and three on neonatal ward admission. As this review included
363 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. Oftentimes, definitions for outcomes were 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(139). 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(140-143). 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(144). 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 5 studies.

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.

We recommend the development COS for fertility sparing surgery in cervical cancer. This review will form the groundwork for the development of this COS. This will reduce unnecessary duplication of research time and provide key stakeholders 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 (28, 145). Delivering COS will facilitate a

480 global approach towards providing high-quality evidence in the field of fertility-
481 sparing surgery for cervical cancer.

482

483 ***Conclusion***

484 Our data highlights heterogeneity in the reporting of outcomes used in studies of
485 fertility-sparing surgery for cervical carcinoma. A defined set of agreed core
486 outcomes is critical to facilitate future studies, for research studies to be meaningfully
487 compared to advise clinical practice and drive forward management change and
488 informed decision making. This systematic review will inform the development of a
489 core outcome set by forming the basis of a Delphi survey, with the addition of data
490 from qualitative work with patients.

491

492 **Table list**

495 **Figure List**

497 **Supplementary Material list**

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. 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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