Abstract

Objectives: To determine women's experiences of brachytherapy for cervical cancer.

Key findings: Nineteen studies were included for data extraction/synthesis. Twelve studies focussed on psychological issues, seven on pharmacological aspects of women's experiences. Themes of anxiety, distress, pain, informational needs and non-pharmacological interventions were found. Nine out of ten psychological studies described brachytherapy as a distressing experience causing anxiety and distress for most women. Non-pharmacological interventions were found to be effective and inexpensive adjuncts. Peri and post-operative pharmacological management was variable, but duration of procedure was an important factor.

Conclusion: Brachytherapy for gynaecological cancer causes varying levels of pain, anxiety and distress. To improve women's experiences there needs to be better pain management, patient information and the development of non-pharmacological interventions. Future recommendations are to develop clinical support guidelines, audit the quality of services and develop effective interventions to improve women's experiences of brachytherapy for locally advanced cervical cancer.

Keywords: Brachytherapy; Cervical cancer; high dose rate; anesthesia; analgesia; anxiety

Highlights:

- Lack of studies examining patient experience in the context of technical advances in brachytherapy.
- Brachytherapy for gynaecological cancer causes varying levels of pain, anxiety and distress.
- Pharmacological approaches should be explored and developed to minimise pain and discomfort
- Non-pharmacological interventions should be explored to improve women's experiences

The experiences of women receiving brachytherapy for cervical cancer: a systematic literature review

Introduction

The worldwide incidence of cervical cancer has been estimated as 528,000 newly diagnosed cases annually and is the 4th most common cancer in women.[1] Global incidence is highest in less developed countries (85%) with higher mortality rates where there is less access to diagnostic and therapeutic health services.[1] Approximately 3,000 new cases of cervical cancer are diagnosed each year in the UK[2]. Despite a comprehensive national cervical screening programme, about a third of these women present with locally advanced disease, unsuitable for surgery. For about 1,000 women per year chemotherapy and radiotherapy including brachytherapy is standard treatment in the UK. Brachytherapy is a type of internal radiation therapy where a radioactive source is placed close to the tumour. To deliver the radiation dose to treat locally advanced cervix cancer, hollow applicators are placed in the uterus and vagina and the radioactive source is passed into the hollow applicators. This technique is currently offered at 42 UK radiotherapy centres.[3]

In the past treatment machines used low dose rate (LDR) radioactive sources with treatment times typically 2-3 days. Treatment was delivered in a shielded radiation room on a ward. Patients were immobilised and in isolation to prevent irradiation of hospital staff. The radiation could be switched off for short periods to allow nursing care, medication delivery and food and drink supplies. However any break in treatment was minimised to keep overall time as short as possible. Visitors were kept to a minimum or prohibited. This was the most common type of brachytherapy in the UK until the early 2000s. Due to lack of availability of replacements for the LDR afterloader caesium sources most UK departments purchased a high dose rate (HDR) afterloader so the treatment could be delivered in minutes[3]. The newer HDR system requires multiple fractions (typically 3-5) to give the equivalent radiobiological effect as LDR treatment.

Recent technical developments include brachytherapy applicators compatible with Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI) to enable acquisition of CT and MRI scans with applicators inside patients. Previously treatment planning was 2-dimensional and dose prescribed to a defined point. However with new treatment planning software 3-dimensional CT and MR images are used to prescribe dose to a volume. With improved imaging and planning it is possible to minimise dose to structures that are sensitive to radiation, known as organs at risk (OARs). Excessive radiation dose to OARs would cause acute and long term side effects. The introduction of extra needle applicators into the cervix tumour has allowed dose escalation which has been shown to increase local tumour control to 85-100%.[4, 5, 6, 7, 8] As the planning has become more complex, with the requirement to draw the tumour (target volume) and OARs onto the 3D images, so the time taken to plan treatments has increased. Anecdotally it is reported that planning time has increased from a matter of minutes to 2-5 hours.

Some centres give HDR brachytherapy as a day case procedure.[9, 10] Patients arrive early in the morning for anaesthetic and theatre procedure for applicator/needle insertion, then CT and/or MR imaging, planning, treatment delivery, applicator removal and discharged home later the same day. Some centres keep patients in hospital overnight with applicators/needles remaining in place and repeat treatments over 2-3 days.[11] Although the patient does not need to remain in isolation in a radiation treatment room like the old LDR treatments, it does mean they have to remain immobile in

bed for a long time. However, their treatment may be completed in one hospital visit and only require one theatre and anaesthetic procedure. Some centres do two treatments for one theatre procedure with one overnight stay, then repeated a week later.[12] Some centres deliver the radiation in pulses, using a source typically 1/10th the activity of a HDR source which is pulsed hourly (Pulsed dose rate, PDR). This is usually given in an isolation room on a ward. The introduction of interstitial needles may have led to the potential for greater pain for women, and some centres have altered their anaesthesia and analgesia techniques to help women cope with this.[10]

There are some benefits and disadvantages for these different methods of dose delivery but the impact of these technical and scheduling changes on patients is unknown. A systematic literature review (SLR) was carried out with the aim to determine women's experiences of brachytherapy for cervical cancer so that consideration could be given to patient's needs.

Methods

The SLR was carried out following PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses),[13] registered on PROSPERO International prospective register of systematic reviews, and completed in May 2017.[14]

A systematic literature search was carried out independently by two researchers. Five databases: MEDLINE; CINAHL; EMBASE; PsychINFO and AMED were selected to ensure journals would be included that were authored and read by oncologists, anaesthetists, psychologists, nurses and radiographers, i.e. all those involved in the care of women during brachytherapy. No restriction to publication date was applied as it was important to include older papers that referred to LDR brachytherapy as the longer duration of treatment may report experiences and coping strategies that are also relevant to newer techniques of HDR brachytherapy with multiple fractions per insertion and PDR brachytherapy. The search strategy was detailed on the PROSPERO entry.[14]

Key terms used for the search are listed in Table 1.

Table 1- Key search terms

Additional sources were searched, including grey literature (Open Grey, GreyNet International, UK Institutional Repository Search and The Healthcare Management Information Consortium), three clinical experts from different professions, snowballing of reference lists of included studies and reverse snowballing to insure that no relevant studies had been missed out. Inclusion criteria were any study which focussed on women's experiences of brachytherapy rather than other factors such as local control, survival or radiation dose planning. Studies were included if their main focus was women's experiences of brachytherapy for gynaecological cancers. As there was no set definition of "patient experience" it was decided by the two researchers that studies where pain scores were reported by the patients would be included. There was no restriction on study design or setting. It was agreed that full text articles were required as abstracts would not contain enough detail for analysis, and English language only could be considered due to prohibitive costs of translation services.

Duplicate studies and those reporting the same cohort of patients were removed. The two researchers independently screened firstly by titles then abstracts to exclude articles that were obviously irrelevant. Full text articles were obtained and full texts in other languages were excluded

at this point. Any disagreement between the two researchers was discussed at the full text stage and any remaining discrepancies discussed with a third party (academic supervisor- third author) to make a final decision. Assessment of the quality of papers was carried out independently by the two researchers using specific Critical Appraisal Skills Programme (CASP) tool for each type of study design.[15] The results were collated, to improve internal validity and reduce risk of subjective bias. Papers deemed as poor quality (more than 75% No or can't tell to CASP tool questions) were excluded before data extraction and synthesis. This step was a change from the method described in the original PROSPERO publication due to the larger than anticipated number of eligible studies and time limitation to complete data extraction and synthesis and to avoid degradation of findings with poor data. A bespoke data extraction tool was created *'a priori'* and data extraction was carried out by one researcher (first author) and checked by the second researcher (second author). Data synthesis was carried out by first researcher, then discussed with the second researcher and agreed upon.

Results

The search strategy produced 727 articles and removing duplicates reduced this to 562. Searching of grey literature produced no additional articles. Screening of titles excluded 438 articles leaving 124. Screening of abstracts excluded 78 articles to leave 44. Full text articles were obtained at this point and snowballing and reverse snowballing found 2 new articles. The 46 full text articles were examined and a further 24 were rejected for the reasons shown in table 2. There were 22 remaining articles. Five studies were randomised controlled studies (RCTs),[16, 17, 18, 19, 20] two case control studies,[21, 22] nine cohort studies,[11, 12, 23, 24, 25, 26, 27, 28, 29] five qualitative studies[30, 31, 32, 33, 34] and 1 systematic literature review.[35]

Table 2- Reason for exclusion from full text

Figure 1. Flow diagram of the literature search and screening process

Critical Appraisal

Critical appraisal with appropriate CASP tools led to exclusion of three studies due poor methodology or not enough information.[22, 29, 35] See Table 3 for summary of the critical appraisal. The three studies excluded at this stage had a large majority (>75%) of negative answers or "can't tell" when the CASP tools were applied. A cohort study by Watanabe Nemoto appears to have recorded pain scores by sending a questionnaire to patients after the procedure had been completed, however sedation was given throughout the procedure.[29] Therefore an overall pain score would be potentially unreliable and likely to indicate whether a woman can remember experiencing pain.[29] Recruitment to this study is unclear as they report that 57 patients received 178 sessions of brachytherapy, however only 74 questionnaires were returned, and the number of women who responded is not reported. The two researchers were unable to understand the method or results of this study. A case control study by Rollison and Strang compared experiences of women undergoing cervical brachytherapy with women having palpation (examination) under anaesthesia for a gynaecological cancer.[22] The LDR brachytherapy meant that women had to lie flat with applicators in place for 15 to 20 hours. The two researchers agreed that the control group was inappropriate and gave no information that would not have been obvious at the outset. For example 8/20 women lying flat for brachytherapy would have preferred an alternative menu compared to 18/20 women in the

control group who approved of the food. This study was considered by the two researchers to be unsuitable to include in data extraction and synthesis. A literature review by Barros and Labate only used 2 search terms and did not include any databases of nursing journals.[35] There was no reported quality assessment of the included studies. The results and discussion are combined and both researchers found the findings were unclear and therefore deemed this study not appropriate for data extraction or synthesis for this SLR.

Table 3 Summary of the critical appraisal.

The nineteen remaining studies included twelve studies focusing on psychological and seven on pharmacological aspects of experiences of brachytherapy. Ten of the twelve psychological studies explored the lived experiences of women undergoing brachytherapy for gynaecological cancer. Two studies investigated interventions to improve the experiences of women during treatment. Themes of anxiety, distress, pain, informational needs and non-pharmacological interventions were found.

Table 4 Characteristics of studies for data extraction and synthesis

Data extraction and synthesis

Anxiety and distress

Of ten studies regarding psychological issues, nine reported that brachytherapy caused anxiety and distress for most women.[12, 23, 26, 27, 30, 31, 32, 33, 34] However Nail found the procedure was well tolerated without high levels of distress, depression or anxiety in most women.[28] Anderson et al described anxiety levels taking a long time to reduce, following completion of treatment.[23] They found that patients' reports of anxiety were higher than assessed by nurses and doctors, which suggests that staff underestimated anxiety and/or that patient's disguised or under-reported anxiety .[23] It was also found that anxiety levels were not reduced prior to the second treatment, concluding that women did not adapt.[23] Kamer et al evaluated influencing factors and found anxiety significantly lower for married or widowed women and those with two or more children.[26] Warnock found incidence and severity of anxiety and distress was variable, presenting a challenge for nurses to provide appropriate care.[34] Kirchheiner et al found that brachytherapy was more stressful than other gynaecological cancer treatments with 30% having acute stress disorder one week after and 41% having post-traumatic stress disorder (PTSD) at three months. Predictive factors for PTSD were a history of sexual violence, poor performance status, higher anxiety levels and lower emotional functioning. Examples of direct quotes from women described the experience as "...like having no chance to defend myself against a rape" and "a debasing situation".[12]

Pain

Experiences of women receiving up to five outpatient HDR procedures described pain as mild to moderate for most but severe for 9%.[27] Significant recall of pain from previous brachytherapy was reported by 29-59% with the amnesic effect being less than anticipated. In contrast to this, distress decreased with each procedure.[27] The duration of the procedure was 2-3 hours with a mean of 127 minutes. A study from South Africa examined HDR brachytherapy with quick outpatient procedures.[30] The women reported negative experiences causing fear, pain and humiliation. They compared brachytherapy to childbirth with high levels of complex pain and described brachytherapy as their "worst experience". The authors recommended better pain management strategies and

non-drug options to complement pharmacological management. They advised minimising observers and staff changes and providing individualised patient information. [30] Another study reported that all participants had varying degrees of pain, but that it was not as bad as expected and that discomfort was experienced as a totality, not limited to pain. [33] Kirchheiner et al reported that pain was the most frequently reported stressful experience during brachytherapy. [12]

Informational needs

Two studies reported women's experiences of lack of information before the procedure. [31, 33] Long et al focussed entirely on informational needs and concluded that women needed more information about their disease, preparation for treatment, the treatment itself, side effects and sexual intercourse. [31] They concluded that information should be delivered verbally and written in the patient's home language.[31]

Pharmacological studies

Seven studies reported investigations of pain medication during gynaecological brachytherapy and are summarised in Table 5. These were published from 1998 to 2017, but all reported on HDR techniques. All studies used a form of the 11 point Visual Analogue scale to record post-operative pain. There were five studies where patients received day case HDR brachytherapy with pain management only required for a few hours.[16, 18, 20, 21, 25] Overall there are a number of different approaches to peri and post-operative pain management, and it is inconclusive which method is superior, but duration of analgesia is a key factor in determining which method is chosen.

Table 5 Pharmacological studies data extraction summary and reviewer comments.

Non-pharmacological interventions

Two studies examined effects of non-pharmacological interventions. Leon-Pizzaro et al investigated the effect of relaxation and guided imagery during brachytherapy on anxiety and depression.[19] This RCT included 66 women receiving LDR brachytherapy for either breast or gynaecological cancer, with two thirds having brachytherapy for gynaecological cancer. Duration of treatment was typically two days. They reported significant reductions in anxiety, depression and body discomfort in the relaxation and guided imagery group compared to the control arm.[19] Chi et al explored the effects of a music relaxation video on pain and anxiety with a RCT of 60 women receiving PDR brachytherapy.[17] They delivered a music relaxation video four times during the first 44 hours of brachytherapy. Perceived pain and anxiety levels were significantly lower in the music relaxation group compared to the control group. They reported a significant reduction in pain after use of the music video indicating that relaxation can reduce pain. [17] Both studies showed significant benefits from their non-pharmacological experimental interventions.

Discussion

Overall the nineteen studies included in this SLR show that brachytherapy causes pain, anxiety and distress and identified a need for better information provision. It was also found that different pharmacological and non-pharmacological approaches can improve women's experiences of brachytherapy. Factors influencing decisions about how to implement dose escalation and reduce toxicity, by implementing new techniques and technological advances to improve local control, are

often based around availability of staff and facilities, such as access to imaging, planning, anaesthetic resources and extra time needed for clinical oncologists, physicists and radiographers. However, the psychological impact for women undergoing the treatment has not been reported as an influencing factor within any reports of implementation of developments or clinical guidelines. The development of HDR brachytherapy from LDR techniques was originally welcomed as an improvement which would allow short day case procedures that would be more tolerable for women. Longer duration for increasingly complex planning requirements, such as extra dose points and constraints for EMBRACE II study[36] and longer treatments such as PDR or multiple HDR fractions per insertion over a number of days would seem likely to increase anxiety and distress. Some studies reported no decrease, or sometimes an increase in anxiety for subsequent insertions and concerns raised that women did not adapt and were not re-assured after their first treatment.[24, 27, 30] Therefore it is possible that multiple day case procedures may lead to a re-traumatisation for women if their first experience of brachytherapy caused distress.

An international survey of practice reported that 97% of 72 respondents used some form of anaesthesia with insertion of brachytherapy applicators[9] and the findings are referred to in the American Brachytherapy Society (ABS) Guidelines general principles.[10] However, only two of the seven pharmacological studies describe analgesia and anaesthesia techniques which would be applicable to centres which deliver HDR brachytherapy with a longer time period with applicators in place.[11, 23] Effective pain management for short procedures taking less than 2 hours in total is unlikely to be applicable for this longer duration technique, or when interstitial needles are added. Local anaesthetic spray onto the cervix or conscious sedation would not provide the required duration of analgesia, especially if interstitial needles are introduced. Wiebe et al suggested that this multi-fraction technique required greater vaginal packing to secure the applicators in place for the prolonged duration when compared with a single fraction technique, and may have contributed to higher levels of pain.[11] Interestingly this centre used PCA opioid pump for post-operative pain control for interstitial techniques and oral/intravenous analgesia for intracavitary techniques, acknowledging that interstitial needles required different analgesia. The use of oral transmucosal fentanyl citrate for brachytherapy procedures has been previously reported.[37] This may provide another option for procedure analgesia or for breakthrough pain at identified points in the procedure likely to cause higher pain, such as transfers for imaging or during applicator removal. Various techniques will be developed in centres with different resources or constraints, and following guidelines may be useful when new techniques are introduced. The Groupe Européen de Curiethérapie and European Society for Radiotherapy & Oncology (GEC-ESTRO), The Royal College of Radiologists (RCR) and ABS guidelines for treatment of locally advanced cervical cancer have been developed. [10, 38, 39, 40, 41, 42] However their main focus is to standardise planning and dose reporting. There is little or no mention of the delivery of clinical aspects relating to patient experience, psychological repercussions and any impact on quality of life after treatment. The use of a standard method of measuring and recording patient's pain scores could assist in auditing and developing best practice for pain management.

The use of non-pharmacological interventions could potentially be introduced to supplement the essential pharmacological approaches and provide women with some control over their own wellbeing during brachytherapy. Relaxation and guided imagery and a music relaxation video showed significant benefits for women undergoing long duration brachytherapy procedures.[17, 19]

They were found to be simple, effective, non-invasive and cheap. Overall it can be surmised that these supplementary interventions may be beneficial to some women during brachytherapy.

Conclusion

There are a multitude of studies reporting technical advances and clinical implications of implementing new developments, but a lack of studies examining patient experiences in this context. This SLR showed that brachytherapy for gynaecological cancer can cause varying levels of pain, anxiety and distress. There is a need for better pain management, patient information and support and the development of non-pharmacological interventions to improve experiences. Pharmacological approaches should be explored and developed to minimise pain and discomfort throughout the procedure, including applicator insertion, patient bed transfers for imaging, waiting between fractions of dose delivery (if multiple doses per insertion) and applicator removal. Alongside optimal management of pain, women's anxiety and distress maybe reduced by non-pharmacological interventions. The development of clinical support guidelines may provide standards to improve women's experiences of the treatment or to facilitate audit to evaluate the quality of service provision, especially when new techniques such as interstitial brachytherapy is introduced. Acquiring patient satisfaction feedback about brachytherapy could also give valuable information about which areas are most distressing or satisfactory and which pharmacological or non-pharmacological support was helpful. This may lead to development of effective interventions (both pharmacological and non-pharmacological) to improve women's experiences of brachytherapy for locally advanced cervical cancer.

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Figure 1

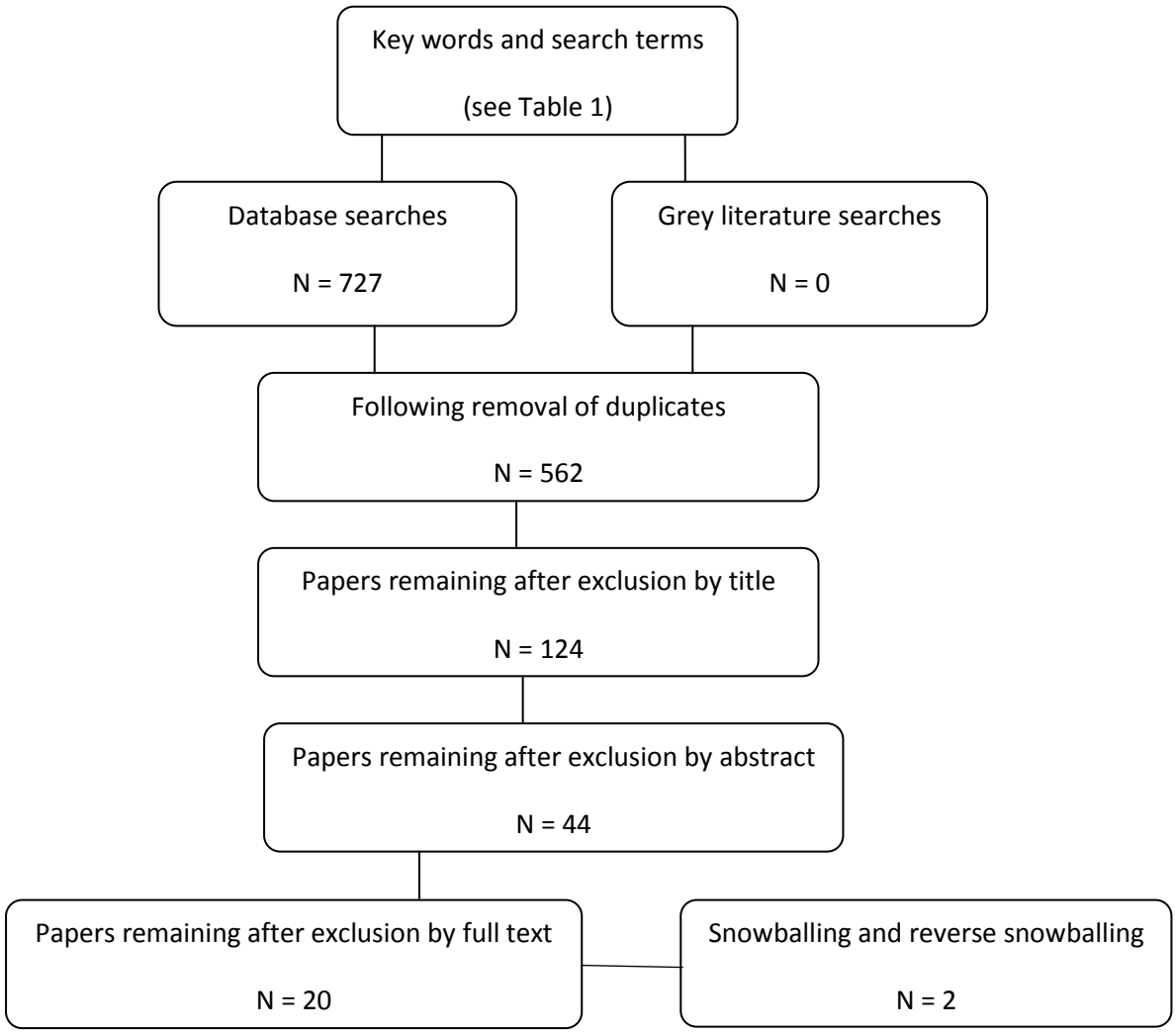
Key words and search terms
(see Table 1)
Database searches
N = 727
Grey literature searches
N = 0
Following removal of duplicates
N = 562
Papers remaining after exclusion by title
N = 124
Papers remaining after exclusion by abstract
N = 44
Papers remaining after exclusion by full text
N = 20
Snowballing and reverse snowballing
N = 2

Figure 1 caption

Figure 1. Flow diagram of the literature search and screening process

Table 1

Table 1- Key search terms

Key words and search extent	Search terms
Cancer, neoplasm or tumour in all text	cancer*, neoplasm*, tumo*
AND	
Cervix or gynaecological in all text	cervi*, gyn*
AND	
Brachytherapy or intracavitary in all text	brachytherapy*, intracavit*
AND	
Anaesthesia, sedation or analgesia in all text	anaesthesi*, anesthesi*, sedat*, analgesi*
OR	
Anxiety, stress, anxious, PTSD, psychology, coping, phenomenon, distress in all text	Anxiet*, stress*, anxious*, ptsd*, psychology*, coping*, phenomen*, distress*

Table 2

Table 2- Reason for exclusion from full text

Reason for exclusion	Number of articles
No full text available- conference abstract/poster only	12
Full text not in English	4
Duplicate discovered (author name different spelling, same patient cohort)	2
Feature article, letter (opinions-not research)	2
Literature study to develop an intervention, no patient data	1
No patient experience found	3

Table 3

Table 3 Summary of the critical appraisal

3a. CASP tool for randomised controlled trials	Chen et al, 1998	Chi et al, 2015	Jain et al, 2007	Leon-Pizzarro et al, 2007	Thanthong et al, 2017
Clearly focussed issue addressed?	Yes	Yes	Yes	Yes	Yes
Assignment of patients randomised?	Yes	Yes	Can't tell	Yes	Yes
Blinded patients, health workers and study personnel?	Can't tell	Not possible	Not possible	Not possible	Yes
Groups similar at start?	Can't tell	Yes	Can't tell	Yes	Yes
Aside from intervention, groups treated equally?	Yes	Yes	Yes	Yes	Yes
All patients accounted for at conclusion?	Yes	Yes	Can't tell	Yes	Yes
How large was treatment effect??	Significant	Significant	Significant	Significant	No difference
How precise was estimate of treatment effect?	$p < 0.001$	Small p values	$p = 0.038$	Small p values	High p values
Results can be applied to the local population?	Partially	Yes	Partially	Yes	Partially
Were all clinically important outcomes considered?	No	Yes	Yes	Yes	Yes
Are benefits worth harms and costs?	Yes	Yes	Yes	Yes	N/A
Suitable quality for data extraction/synthesis	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*

3b. CASP tool for cohort studies	Amsbaugh et al, 2016	Anderson et al, 1984	Bhannabhai et al, 2013	Kamer et al, 2007	Kirchheiner et al, 2014	Kwekkeboom et al, 2009	Nail, 1994	Watanabe Nemoto et al, 2015	Wiebe et al, 2011
Clearly focussed issue?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cohort recruitment acceptable?	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	No	Yes
Exposure accurately measured to minimise bias?	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Outcome accurately measured to minimise bias?	Can't tell	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Important confounding factors identified?	Mostly	Mostly	No	Yes	Yes	N/A	Yes	No	Yes
Confounding factors in design/analysis?	No	No	No	Yes	Yes	N/A	Yes	No	Yes
Follow up complete enough?	N/A	Yes	No	Yes	Yes	Yes	Yes	Can't tell	Yes
Follow up long enough	N/A	No	No	No	No	No	Yes	Yes	Yes
Clear results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Precise results?	Yes	Yes	Can't tell	Can't tell	Yes	Yes	Yes	No	Yes
Believable results?	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	No	Can't tell
Results can be applied to the local population?	Partially	Partially	Partially	Can't tell	Partially	Partially	Yes	No	Yes
Results fit with other evidence?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes
Value to practice?	Yes	Yes	Limited	Yes	Yes	Yes	Yes	No	Yes
Suitable quality for data extraction/synthesis	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Yes*

3c. CASP tool for qualitative research	Velji & Fitch, 2001	Warnock, 2005	So & Chui, 2007	Dzaka et al, 2016	Long et al, 2016
Clear statement of aims?	Yes	Yes	Yes	Yes	Yes
Qualitative methodology appropriate?	Yes	Yes	Yes	Yes	Yes
Research design appropriate?	Yes	Yes	Yes	Yes	Yes

Recruitment strategy appropriate?	Unknown	Unknown	Yes	Unknown	Yes
Data collection clear/justified?	Yes	Yes	No	Yes	Yes
Relationship between researcher & participants considered?	Yes	No	Yes	Partial	Yes
Ethical issues considered?	Yes	Unknown	Yes	Yes	Yes
Data analysis sufficiently rigorous?	Yes	No detail	Yes	Yes	Yes
Clear statement of findings?	Yes	Yes	Yes	Yes	Yes
Research valuable to current practice/policy/literature?	Yes	Yes	Yes	Yes	Yes
Suitable quality for data extraction/synthesis	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*

3d. CASP tool for case control studies	Isoyama-Shirakawa et al, 2015	Rollison & Strang, 1995
Clearly focussed issue?	Yes	Yes
Appropriate method?	Yes	No
Recruitment strategy appropriate?	No	No
Acceptable selection of controls?	Yes	No
Exposure accurately measured to minimise bias?	Yes	No
Important confounding factors identified?	Yes	No
Confounding factors in design/analysis?	Yes	No
Clear results?	Yes	Yes
Precise results?	Yes	Yes
Believable results?	Limited	Yes
Results can be applied to the local population?	Partially	No
Results fit with other evidence?	Yes	Can't tell
Suitable quality for data extraction/synthesis	*Yes*	*No*

3e. CASP tool for systematic review studies	Barros & Labate, 2008
Clearly focussed question?	Yes
Appropriate papers searched?	No
Were all relevant studies included?	No
Sufficient quality assessment?	No
Combined results appropriate?	N/A
Clear results?	No
Precise results?	No
Results can be applied to the local population?	Can't tell
Were all important outcomes considered?	No
Are benefits worth harms and costs?	Can't tell
Suitable quality for data extraction/synthesis	*No*

Table 4

Table 4 Characteristics of 19 studies for data extraction and synthesis in date order

AUTHOR	PUBL DATE	COUNTRY	STUDY DESIGN	LDR/HDR/ PDR
Anderson et al[24]	1984	USA	Cohort study, prospective	LDR
Nail et al[28]	1993	USA	Cohort study, prospective	LDR
Chen et al[16]	1998	China	Randomised controlled trial	HDR
Velji and Fitch[33]	2001	Canada	Qualitative, phenomenology	LDR/PDR
Warnock, C[34]	2005	UK	Qualitative study, prospective	HDR
Jain et al[18]	2007	India	Randomised controlled trial	HDR
Kamer et al[26]	2007	Turkey	Cohort study, prospective	HDR
Leon-Pizzarro et al[19]	2007	Spain	Randomised controlled study	LDR
So and Chui[32]	2007	Hong Kong	Qualitative study	LDR
Kwekkeboom et al[27]	2009	USA	Cohort study, longitudinal descriptive	HDR
Wiebe et al[11]	2011	Canada	Cohort study, prospective	HDR
Bhanabhai et al[25]	2013	Canada	Cohort study, retrospective observational	HDR
Kirchheiner et al[12]	2014	Austria	Cohort study, prospective observational pilot	HDR
Chi et al[17]	2015	USA	Randomised controlled trial	PDR
Isoyama-Shirakawa et al[21]	2015	Japan	Case control study- retrospective	HDR
Amsbaugh et al[23]	2016	USA	Cohort study, retrospective	HDR
Dzaka and Maree[30]	2016	South Africa	Qualitative study, descriptive	HDR
Long et al[31]	2016	South Africa	Qualitative, prospective, phenomenology	HDR
Thanthong et al[20]	2017	Thailand	Randomised controlled trial	HDR

Table 5

Table 5 Pharmacological studies data extraction summary

Author	Study Aim	Study design	Population/context	Intervention	Results	Authors Recommendations	Reviewers comment
Chen et al, 1998	To investigate the effect of local vaginal anaesthesia on pain relief and safety by monitoring serum levels	RCT	40 patients with cervical cancer, 5 treatments each. Short duration-outpatient procedure	GA for 1st trt. Then randomised to trt-control-trt or control-trt-control-trt. Trt: lidocaine 10% sprayed onto cervix for 5 mins. Control-Placebo spray. Meperidine injection for all. No GA	10% lidocaine solution significantly decreased degree of painful sensation. Mean pain score 49.9 ± 24.1 SD; control mean 60.1 ± 24.8 SD. Sig difference P<0.001. No diff in physiological response or adverse effects. Serum levels didn't rise to unsafe levels.	Safe and effective method for analgesia.	Still had mean moderate pain scores compared with GA or spinal/epidural. Only suitable for short duration procedures.
Jain et al, 2007	To compare 3 different anaesthetic techniques, quality of analgesia and side effects.	RCT	35 women with cervical cancer, divided into 3 arms, Typically 1½ - 2 hours overall time, 3 treatments each, 1 per week.	Group A- subarachnoid block, Group B- GA with laryngeal mask airway, Group C - GA with face mask. Measured pain, motor block, sedation level, nausea and vomiting and post-operative analgesia requirements.	Significantly less analgesia required by group A. P = 0.038. No sig difference in post op nausea and vomiting. No sig diff in sedation level. Overall 24.7% had mild pain, 18.1% moderate pain and 5.7% severe pain. Higher complication rates with GA.	Regional anaesthesia provides better post op analgesia than GA.	Difficult to know if this could be applicable to longer duration schedules, PDR and multiple HDR trts per insertion.
Wiebe et al, 2011	To assess adequacy of analgesia and symptom control with multiple fractions of HDR brachy during a single applicator insertion	Prospective cohort	18 patients with gynaecological cancers recruited. Data from 17. 14 intracavitary and 3 interstitial. Typical duration 25-36 hrs.	GA for insertion. Transferred to oral or subcut anaesthesia after GA. Interstitial had PCA pump after GA. Tolerability assessed by pain scores, anxiety and nausea, 5 time points: baseline, transfer to CT couch, after 1st trt, immediately after applicator removal, follow up (time point not specified).	Mean pain scores highest after CT transfer 3.3 ± 2.6 SD. Was 0.9 ± 1.7 SD at baseline. 5 pts reported no pain. Not sig higher pain with interstitial, 3.3 vs 2.3, P=0.42. Anxiety score highest before brachy 4.3 ± 3.4. During procedure resolved to 1.3 ± 1.6 SD. Slightly higher at FU appt 1.6 ± 1.5 SD. Nausea mode score = 0. Severe pain (7-10) in 4/17 pts, all at CT transfer + 1 after trt delivery, 1 at FU appt. Also 3 pts had severe anxiety, all at baseline.	Overall only mild pain and anxiety. Discussed anticipatory anxiety. Pre-emptive analgesia at specific points. Consider studies on management of emotional distress such as guided imagery or music relaxation.	Underestimate/ignoring severe pain- reported in 4/17 at specific time point. Small number of participants. Overall good pain management therefore applicable to longer duration procedures.

Bhanabhai et al, 2013	To assess the effectiveness of conscious sedation	Retrospective observational	20 patients with cervical cancer, 57 procedures. Weekly outpatient procedure. Median duration 1.4 hours.	Pain scores recorded every 10 mins and at key points during HDR brachy procedure. Qualitative notes by nursing staff. Satisfaction with pain control recorded in recovery room. Midazolam and opioid used.	Good pain control achieved with conscious sedation. Brief moments of moderate to severe pain mostly when ring and tandem applicator inserted. Maximal pain ranged from 0-10, mean 4.7. All pts satisfied with pain control.	Effective regime. Fentanyl now opioid of choice as fast onset and rapid clearance.	May only be suitable for short duration procedures. Patient satisfaction scoring not explained.
Isoyama-Shirakawa et al, 2015	To investigate the effects of caudal epidural anaesthesia	Retrospective case control	34 women with cervical cancer. Control group, earlier time period, 30 pts cervical cancer, same applicator. 4 trts in control group, 5 in anaesthesia group, no duration but likely to be short outpatient trt	Experimental group had caudal epidural with mepivicaine + other analgesia or sedation. Control group had analgesia and sedation only- no anaesthesia.	Caudal epidural success rate 97%. Patient reported pain scores sig less for anaesthesia group (P=0.038 and P=0.037). Outcomes from 30 pts only. Mean score 5.17 ± 2.97 SD vs 6.8 ± 2.59 SD (P=0.035). Lower use of sedation but higher use of opiates in anaesthesia group. No complications from caudal.	Caudal is an option for safe and effective regional anaesthesia.	High levels of pain in caudal epidural group compared to other studies. May not have blocked pain caused by applicators in uterus. May give better block for cervix, vagina and perineum, not uterus. Could be applicable to short brachy procedures, not PDR or HDR with multiple trts per insertion.
Amsbaugh et al, 2016	To determine optimal epidural anaesthesia for interstitial brachy for gynaecological cancers	Retrospective cohort	71 patients with gynae cancers (35 cervix, 16 vagina, 13 uterus, 7 vulva), Interstitial brachytherapy	3 arms: 12 ropivocaine only; 59 opioid + ropivicaine. Subgroup: 14 fentanyl + ropivicaine; 45 hydromorphone + ropivicaine	More pain in ropivicaine only group, needed more additional opiates, suggests inadequate pain control.; no difference in nausea	Combined modality epidural improves pain control, opioid with local anaesthetic, compared with local anaesthetic alone	All Interstitial cases, but analgesic technique may still be applicable to Intracavitary or hybrid techniques.
Thanthong et al, 2017	To compare the effectiveness of two sedative regimens in relieving pain	RCT, double blind crossover	40 pts, 160 treatments, all cervical cancer 4 treatments each, typically 2-3 hours.	Benzodiazepine to all, then 2 x fentanyl and 2 x meperidine. Researchers, HCPs and patients blinded. Pain score before intervention and every 15 minutes. If pain score >4 then an	Treatment effect- no sig difference in effectiveness of sedation types. Pain peaked at 45 minutes. Most experienced moderate pain during procedure, similar to other studies.	No significant difference therefore cheapest sedation is appropriate.	Applicable for day case HDR brachy, but not for multiple # as duration too long.

				additional opioid was given. QoL using EQ-5D.			

Abbreviations key: RCT Randomised controlled study; GA general anaesthetic; trt treatment; pts patients; gynae gynaecological; SD = Standard Deviation