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Vaginal dilator therapy for women receiving pelvic radiotherapy (Review)

Miles T, Johnson N

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[Intervention Review]

Vaginal dilator therapy for women receiving pelvic radiotherapy

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ABSTRACT

Background

Vaginal dilation therapy is advocated after pelvic radiotherapy to prevent stenosis (abnormal narrowing of the vagina), but can be uncomfortable and psychologically distressing.

Objectives

To assess the benefits and harms of different types of vaginal dilation methods offered to women treated by pelvic radiotherapy for cancer.

Search methods

Searches included the Cochrane Central Register of Controlled Trials (CENTRAL 2013, Issue 5), MEDLINE (1950 to June week 2, 2013), EMBASE (1980 to 2013 week 24) and CINAHL (1982 to 2013).

Selection criteria

Comparative data of any type, which evaluated dilation or penetration of the vagina after pelvic radiotherapy treatment for cancer.

Data collection and analysis

Two review authors independently assessed whether potentially relevant studies met the inclusion criteria. We found no trials and therefore analysed no data.

Main results

We identified no studies for inclusion in the original review or for this update. However, we felt that some studies that were excluded warranted discussion. These included one randomised trial (RCT), which showed no improvement in sexual scores associated with encouraging women to practise dilation therapy; a recent small RCT that did not show any advantage to dilation over vibration therapy during radiotherapy; two non-randomised comparative studies; and five correlation studies. One of these showed that objective measurements of vaginal elasticity and length were not linked to dilation during radiotherapy, but the study lacked power. One study showed that women who dilated tolerated a larger dilator, but the risk of objectivity and bias with historical controls was high. Another study showed that the vaginal measurements increased in length by a mean of 3 cm after dilation was introduced 6 to 10 weeks after radiotherapy, but there was no control group; another case series showed the opposite. Three recent studies showed less stenosis associated with prophylactic dilation after radiotherapy. One small case series suggested that dilation years after radiotherapy might restore the vagina to a functional length.

Authors' conclusions

There is no reliable evidence to show that routine, regular vaginal dilation during radiotherapy treatment prevents stenosis or improves quality of life. Several observational studies have examined the effect of dilation therapy after radiotherapy. They suggest that frequent dilation practice is associated with lower rates of self reported stenosis. This could be because dilation is effective or because women with a healthy vagina are more likely to comply with dilation therapy instructions compared to women with strictures. We would normally suggest that a RCT is needed to distinguish between a casual and causative link, but pilot studies highlight many reasons why RCT methodology is challenging in this area.

PLAIN LANGUAGE SUMMARY

Vaginal dilator therapy for women receiving pelvic radiotherapy

Background

Pelvic radiotherapy for gynaecological (uterine, cervical, vaginal) and anorectal cancer may damage the vagina. It may cause the vagina to shrink and can make the sides stick together. It has become established practice to recommend regular vaginal dilation after radiotherapy to reduce or prevent this risk. Dilation involves inserting and rotating a phallus-shaped appliance in the vagina approximately three times a week for about five minutes to stretch the skin.

Review question

This updated review re-appraised all the literature and retrieved all available data on this topic to see if there was any evidence to support vaginal dilation after pelvic radiotherapy.

Main or key findings

Women who want to preserve the length of their vagina after radiotherapy should consider dilation. There are limited data from observational studies that suggest regular stretching of the vagina, once radiotherapy treatment is completed, might reduce the risk of scaring by a small amount. There is no evidence to support dilation therapy during radiotherapy. There are also case reports and one case series suggesting that dilation months or years after radiotherapy might help restore vaginal length.

Quality of the evidence

Randomised trial design has not, and may never, obtain high-quality evidence to assess vaginal dilation therapy. The available studies suggest, but cannot prove, that dilation works. However, this only applies once the radiotherapy has finished. There is an association between vaginal dilation after radiotherapy and less vaginal stenosis, but this is not proof that the benefit is due to dilation. The link between dilation and less stenosis could either be due to a beneficial effect of dilation or because women with stenosis (or who self report stenosis) are less able to use the dilator.

BACKGROUND

Description of the condition

Cancer of the uterus and cervix often involves treatment with pelvic radiotherapy. A permanent side effect of radiotherapy is vaginal dryness, vascular and tissue damage, thinning of the epithelium and atrophy of the vagina, with a reduction in elasticity and development of fibrosis (Abitol 1974; Cartwright 1995). About a third of women suffer from vaginal stenosis (obstruction by scar tissue) after pelvic radiotherapy (Abitol 1974; Bertelesen 1983; Hartman 1972; Seibel 1982; Vasicka 1958) and altered vaginal epithelium (skin) causing sexual dysfunction (Denton 2000), but the range of reported incidence varies from 1.2% (Eltabbakh 1977) to 88% (Hartman 1972). The anatomical deformity of the vagina contributes negatively to a woman's well-being. Any therapy that minimises the impact of radiation damage might improve sexual recovery for women after treatment. Another important reason to prevent vaginal stenosis, even for women who are not, or do not plan to be, sexually active, is that the vagina needs to be kept patent (open) to enable adequate examination in the five-year follow-up period to detect treatable recurrence of the cancer.

Description of the intervention

Surveys show that vaginal dilation with radiotherapy is standard British practice (White 2006), and the UK guidelines from the National Gynaecological Oncology Nurse Forum recommended dilation "three times weekly for an indefinite time period" (UK Nurse Forum 2005). The UK patient charity Macmillan advises patients that they "may use a dilator during radiotherapy treatment or afterwards" (Macmillan 2014a; Macmillan 2014b). Australian guidelines recommend dilation after brachytherapy "as soon as comfortably possible" and "certainly within four weeks" and "for three years or indefinitely, if possible" (Best Clinical Practice Guidelines 2009), but the uptake of these guidelines is variable (Lancaster 2004). USA practice guidelines are different and the NCI 2009 suggests that "doctors may advise their patients not to have intercourse during radiation therapy". The original Cochrane review stimulated the formation of a guideline group within the International Gynaecological Cancer Society (IGCS) (Miles 2010a). This recommended routine regular vaginal dilation after the inflammatory phase of radiotherapy had settled for two years, or at the clinician's discretion (Miles 2012c). Guidelines from Australia instruct women that the minimum use is three times weekly for an indefinite time period (Carter 2012). These guidelines state that some cancer centres encourage the use of dilators during treatment, but all women are advised to start using dilators regularly following their treatment. Most centres offer a vaginal dilator manufactured as a medical device. Whilst some use graded glass, vulcanite or opaque plastic models, the majority provide dilator sets of four graduated sizes moulded in rigid plastic or silicone (Amielle 2010; MEDintim 2010; Soul 2010).

How the intervention might work

Skin will grow when it is stretched and this is the principle behind tissue expansion in plastic surgery (Johnson 1990). Observational studies of women born with no vagina (vaginal agenesis) show that the vagina can be stimulated to stretch and re-grow, if pressure is applied to the skin. Fingers, a dilator, stent, phallus or any other phallic-shaped device can be used (Johnson 1991). It has been assumed that dilation could be used after or during radiotherapy to reduce the consequential fibrosis. Dilation might separate the adhesions formed by the denuded epithelium, thus possibly preventing stenosis (Faithfull 2003; Hassey-Dow 1992; Krumm 1993; Rice 2000). However, it is also plausible that stretching the vagina during the inflammatory phase of radiotherapy treatment might cause additional scarring and promote additional damage, both physically and psychologically. Furthermore, translating the physiology of normal young epithelial cells and assuming that this new growth potentially applies to irradiated skin may be naive. It is possible that regular stretching of recently irradiated and inflamed skin causes micro tears and the associated additional inflammation could cause more (not less) scarring (Bentzen 2006; Denham 2002).

Why it is important to do this review

Routine vaginal dilation during and after radiotherapy is advocated in many guidelines, review articles (Cartwright 1995; Crowther 1994; Davidson 2003; Gosselin 2001; Grigsby 1995; Hartman 1972; Lamberti 1979; Pountney 2005; Wilmoth 2000), and by patient advocates. Routine vaginal dilation is advocated by 97% (64/65) of UK radiotherapy centres, but only 48% of women feel they can comply with instructions (Faithfull 2003; White 2004). It is important to know if the intervention during or after radiotherapy is beneficial, because the intervention requires valuable nursing and therapy radiographer time. In addition, many women describe it as a negative experience (Bonner 2012), with deep psychological and emotional implications linked to the intrusive nature of dilation (Cullen 2012). Finally, dilators have been linked to rectovaginal fistulae (Hoffman 2003). It follows that a full systematic review is required to guide clinicians who may want to prescribe adjuvant dilation associated with pelvic radiotherapy.

The treatment and prevention of stenosis is an important aspect of cancer care and this review examines all the available data on dilation practice to inform clinicians on the value of this strategy.

OBJECTIVES

To assess the benefits and harms of different types of vaginal dilation methods offered to women treated by pelvic radiotherapy for cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Initially we intended to focus on randomised controlled trials (RCTs), quasi-RCTs and cohort studies where the comparability of cohorts had been established or existing confounding factors adjusted. The first search revealed insufficient data to draw any inferences. Subsequently, we repeated and expanded the search to capture case control retrospective studies, longitudinal surveys and case histories. A summary of studies containing any comparative data on vaginal dilation following radiotherapy or any characteristics of data on vaginal dilation following radiotherapy can be found in Table 1.

Types of participants

The systematic examination of the literature focused on women confirmed to have a pelvic malignancy who had received pelvic radiotherapy as part of their treatment schedule. This could be

either primary radiotherapy or postoperative radiotherapy, with or without chemotherapy or palliative therapy.

Types of interventions

We considered medical devices and commercially available devices. This included all types of vaginal dilation therapy, such as digital dilation with lubrication, speculums, medical devices or vibrators.

Types of outcome measures

Primary outcomes

- Sexual satisfaction.
- Vaginal trauma later redefined as vaginal stenosis.

Secondary outcomes

- Concordance with the intervention (data extracted as non-compliance).
- Any other measure of sexual function at any time.
- Psychosexual morbidity at any time.
- Quality of life (QoL) (EORTC 1995), at any follow-up visit.
- LENT-SOMA score of stenosis (Pavy 1995), at any time.

We did not consider pain and infection as outcomes, since we thought it unlikely that such data would be available and indeed did not find any. However, these might be included as outcomes in any future update.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

- the Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register (June 2013);
- the Cochrane Central Register of Controlled Trials (CENTRAL 2013, Issue 5);
- MEDLINE (from 1950 to end 2008 and then updated to June week 2, 2013);
- EMBASE (from 1980 to end 2008 and then updated to week 24 2013); and
- Google and Google Scholar (up to November 2008 and then updated to July 2013).

The MEDLINE, CENTRAL and EMBASE search strategies are listed in Appendix 1, Appendix 2, and Appendix 3. The Google search used 'vaginal stenosis dilation radiotherapy'.

We excluded intervention terms because their inclusion might have lost some relevant papers. We conducted searches to identify RCTs and non-RCTs comparing interventions related to vaginal dilation therapy and pelvic radiotherapy. The search strategy identified studies in all languages and, when necessary, we intended to review non-English language papers and translate them for potential inclusion in the review. Since 2008, ongoing monthly reviews and automatic alerts of new papers have been established.

Searching other resources

Unpublished and grey literature

We contacted the main investigators of any relevant ongoing trials for further information, as well as major co-operative trials groups active in this area.

Handsearching

We handsearched reports of conferences in the following sources:

- Annual Meeting of the British Gynaecological Cancer Society (BGCS);
- Annual Meeting of the International Gynecologic Cancer Society (IGCS);
- Annual Meeting of European Society of Medical Oncology (ESMO);
- Annual Meeting of the American Society of Clinical Oncology (ASCO);
- Annual Meeting of the European Society of Gynaecological Oncology (ESGO); and
- Annual General Meeting of the UK National Forum of Gynaecological Oncology Nurses (NFGON).

Reference lists and correspondence

We checked the citation lists of included trials and contacted experts in the field to identify further reports of trials. We had personal contact with the following sources:

- the Cochrane Gynaecological Cancer Review Group;
- the Gynae Oncology Nurse Forum Dilator Subgroup;
- a gynaecology patient user group by letter (via newsletter); and
- the authors of the included trials (by direct e-correspondence).

Data collection and analysis

The review authors independently manually reviewed all titles and abstracts retrieved by electronic searching. We excluded those studies that clearly did not meet the inclusion criteria. We obtained copies of the full text of potentially relevant references and assessed these independently. We found no trials that met the inclusion criteria and documented the reasons for excluding studies (Excluded studies). If there are any randomised trials that could be included in future updates, we will use the methods found in the Differences between protocol and review section.

RESULTS

Description of studies

Results of the search

The original electronic search in 2008 identified 246 original papers and many duplicates. We retrieved a further reference by hand cascade searching, which was not in the electronic searches (Velaskar 2007). Seven articles were potentially relevant and we retrieved them in full. We identified updated versions of relevant trials. The full-text screening of these studies found no trials examining our primary outcomes in a high-quality comparative trial of dilation versus no dilation. The electronic updated search in June 2013 identified an additional nine (MEDLINE) and 84 (EMBASE) papers. Five had useful data; all were known to the authors. It also added two useful studies examining the psychological effects

of dilation therapy. There were no new reports in CENTRAL or the Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register.

Included studies

There are no randomised trials comparing dilators versus no dilators.

Excluded studies

Fourteen studies that examine vaginal dilation failed to meet the inclusion criteria. These included three RCTs, nine observational studies and two ongoing studies. The Characteristics of excluded studies and Characteristics of ongoing studies tables provide reasons for the exclusion of all the studies. Brief descriptions of the studies are given below.

Randomised controlled trials

One randomised controlled trial (RCT) compared dilators with vibrators (Miles 2012a). This study randomised women to dilation therapy with either a static or vibrating dilator to be used during radiotherapy. There was no difference in outcome attributable to randomisation between the groups, but this study had a high drop-out rate and suffered from recruitment bias.

Two other RCTS examined the adherence to dilation therapy following a psycho-educational programme. Both studies showed that there was a small increase in the use of dilation therapy in women who were randomly allocated to motivational support (Jeffries 2006; Robinson 1999). Robinson 1999 showed that women who dilated more often did not have improved sexual function scores.

Observational studies

There were nine observational studies. Four studies tested the association between stenosis and the number of times a woman reported she used dilation therapy (Bahng 2012; Gondi 2012; Law 2013; Miles 2012b); one compared a speculum examination with topical mitomycin with no therapy (Sobotkowski 2006); one was a study with historical controls (Decruze 1999); and two were observational non-comparative case studies (Poma 1980; Velaskar 2007). These are described in Table 1. The nine observational studies that comment on vaginal toxicity have been excluded from formal analysis for one of the following reasons:

- was a case series of only five women (Poma 1980);
- no relevant data were available (Bruner 1993);
- historical controls were used to compare with the intervention group (Decruze 1999);
- the focus was on the application of mitomycin with a speculum (Sobotkowski 2006);
- there was no control group and therefore we do not know what would have happened if dilation had not been suggested (Velaskar 2007);
- was a survey of measured vaginal length and elasticity in women who had had radiotherapy (Miles 2012b);
- were case series that correlated the chance that women with stenosis would be associated with dilation therapy (Bahng 2012; Gondi 2012; Law 2013).

Ongoing studies

We know of two ongoing studies (Bruner 2011; NCI UP 10G01). Both are similar to the trial by Jeffries 2006 and more details are in the Characteristics of ongoing studies table.

Risk of bias in included studies

No trials met our inclusion criteria and therefore we did not apply the 'Risk of bias' tool. The only available data come from non-randomised trials. These are associated with a high risk of bias and are classified as low-level evidence with a critically high risk of bias.

Effects of interventions

It was not possible to carry out a meta-analysis from the data collected.

DISCUSSION

Summary of main results

No studies met our inclusion criteria and the following discussion is based on evidence from excluded studies. Some women with a stenosis of the vagina years after radiotherapy can regain patency with dilation therapy. This is shown by case reports where women who had not had any vaginal penetration for a number of years after radiotherapy were able to regain length and function with dilation (Poma 1980). Case series (Velaskar 2007), correlation analysis (Bahng 2012; Gondi 2012; Law 2013) and comparisons with historical controls (Decruze 1999) suggest that women who dilate their vagina after radiotherapy seem to have less stenosis. In contrast, studies that assessed dilation therapy during radiotherapy failed to show any benefit (Miles 2012b; Miles 2012a; Robinson 1999; Sobotkowski 2006) (Table 2).

Overall completeness and applicability of evidence

We used a comprehensive search to identify all studies relevant to this subject. In the absence of included studies, we discuss the available evidence, whilst recognising that this is of critically high risk of bias. We would encourage readers who might be aware of further studies to use *The Cochrane Library* feedback system to bring these to our attention.

Quality of the evidence

No studies met the inclusion criteria for the review.

Of the excluded studies discussed, one small randomised controlled trial (RCT) suggests that dilation therapy does not improve sexual function (Miles 2012a). This study has a small sample size, the participants were a mixture of older and younger women and the pathologies were a mixture of cervical and uterine cancer. Sexual function was difficult to measure with any precision, the analysis by intention-to-treat was contaminated by cross-over and the control group received a good standard of care. These features of the study might have contributed to minimise any potential difference associated with the intervention and the power of the trial was insufficient to detect any small differences in the groups. The other RCT showed that motivational techniques could increase the number of women using dilation therapy but the additional numbers were small and sexual function scores were not a primary objective of the study (Robinson 1999).

The review highlighted four good surveys of self reported dilation correlated with a better vaginal outcome (Bahng 2012; Gondi 2012; Law 2013; Velaskar 2007). This shows an association between dilation and less stenosis. Whilst the observation could mean that dilation does improve vaginal calibre, it could also mean that women who dilate do so because they have a good capacity and pain-free genital tract. Women who dilate less frequently may do so because they are more likely to have pain, inflammation and strictures. These factors make randomisation critical to avoid selection bias.

However, one reason for the paucity of data is that it is practically difficult for researchers to carry out scientific evaluations of the vagina during radiation treatment. There are a handful of observational reports that support adjuvant dilation practice. The main focus of these reports is that dilation enables a woman to tolerate a larger sized dilator in her vagina at the end of therapy. Most observational data support the possibility that dilation after radiotherapy treatment may be associated with a lower risk of stenosis, but a therapeutic role for dilation has not been demonstrated. The survival analysis in Gondi 2012's survey is more persuasive, since dilation practice was recorded before the stenosis developed, implying that the result was not just due to women refraining from dilation simply because it was unpleasant. However, the lack of unbiased data means that we can draw no firm conclusions about cause and effect.

Potential biases in the review process

No data were found that met our inclusion criteria. The excluded studies are at high risk of bias. In non-randomised studies, the use of dilators may be a surrogate for improved vaginal capacity without treatment and women with vaginal toxicity are less likely to report that they use a dilator in their vagina. This is not proof of an effect and does not show that dilation prevents stenosis. RCTs failed to show any difference in any surrogate outcomes (Miles 2012a; Robinson 1999). However, both RCTs lack statistical power.

We conducted a thorough review of the literature and searched for published and unpublished studies. One potential bias in the review process is that the review author (TM) is the lead author for a number of articles in this area. However, since no studies were included for analysis, there was no conflict of interest in data extraction and analysis.

Agreements and disagreements with other studies or reviews

Numerous clinical reviews recommend routine dilation, but do not offer supporting data (Cartwright 1995; Crowther 1994; Davidson 2003; Grigsby 1995; Gosselin 2001; Hartman 1972; Lamberti 1979; Pountney 2005; Wilmoth 2000). It is possible that these recommendations have been uncritical in their acceptance of past teachings based on the observation that dilation helps women born with no vagina and may help women with vaginismus. However, some reviewers do reference their recommendation. Examples include Burke 1996, who refers the readers to a comparison of American and French practice. This reference is a commentary on the variations between nations and does not offer supporting data for the practice. Krumm 1993 and Lamberti 1979 also advocate dilation and they support their recommendation by referring readers to the 1986 guidelines on implant therapy from Ellis Fischel State Cancer Center, Columbia. This has no citation and is a description of local practice that has no supporting data. The previous Cochrane Review (Denton 2003) relied on the paper by Decruze 1999 to conclude that the evidence for dilation "was sufficient to endorse the widespread use of vaginal dilators". Decruze 1999 implies that dilation prevents stenosis, but critical appraisal reveals that the study examined historical controls, who still might have used a dilator, and the 35 cases in each arm were not blinded nor well matched.

Not all reviewers accept that dilation is effective. The review by Abitol 1974 was more analytical than most text books. They say that "mechanical dilation of the vagina and the use of topical oestrogens appear to be of doubtful value". Australian practice is less protocol-driven than UK practice. A survey shows that local practice tends to be dominated by the non-scientific opinion of the leading clinician (Lancaster 2004). USA practice guidelines comment that "Doctors may advise their patients not to have intercourse during radiation therapy" (NCI 2009), and American practice guidelines do not promote dilation therapy. New surveys of the psychological impact associated with dilation also recommend caution. However, three surveys have published data associating dilation with a better outcome (Bahng 2012; Gondi 2012; Law 2013). Gondi 2012 followed the risk of stenosis over time. Their data suggest that the association cannot be explained by saying that dilation compliance is only dependant on the ease of dilation.

AUTHORS' CONCLUSIONS

Implications for practice

No good-quality studies were included in his review to inform practice in this area. Of the excluded studies, Robinson 1999 and Miles 2012a are the only studies that examined sexual function in women who were randomly allocated to more dilation therapy compared to less. Neither supported dilation therapy during radiotherapy. The psychological trauma induced by dilation is very variable and is difficult to measure. However, anecdotal evidence suggests that dilation can inflict psychological (Bonner 2012; Cullen 2012; Miles 2007) and physical damage (Hoffman 2003). Possible harm and the absence of benefit from dilation therapy during radiotherapy should mean that dilation should not be practised during radiotherapy treatment. However, new reports of dilation once radiotherapy is completed do support dilation therapy, provided it is started once the acute inflammation induced by radiotherapy has settled. Dilation therapy after radiotherapy can also be used to treat established stenosis in some women (salvage therapy). Dilation after radiotherapy may have prophylactic value, but this belief is based on studies at critically high risk of bias. It may be unnecessary in women who are sexually active because they are having surrogate dilation therapy. Guidelines to encourage dilation therapy may have limited effect because of the low number of women who comply with instructions. Finally, it is stressful for some women and routine prophylaxis may be unnecessary as any subsequent stenosis may be redeemable later.

Implications for research

Previous reviews have concluded that there are no good data examining the benefits of routine dilation of the vagina during or soon after pelvic radiotherapy (Johnson 2010; Miles 2010b). Three good surveys have recently been presented and these show an association between less stenosis and greater dilation frequency, if dilation is commenced after completion of the radiotherapy course

(Bahng 2012; Gondi 2012; Law 2013). These studies did not meet our inclusion criteria. They are not randomised and consequently at high risk of bias. The Miles 2010b review argued for randomised trials of dilation practice during the recovery phase to help inform practice. A pilot study testing a randomised trial protocol revealed some fundamental difficulties with designing studies to evaluate dilation therapy (Miles 2012a). These will need to be addressed in future trials and are summarised below.

- There is a high likelihood of cross-over between groups.
- There is interference in the effect of underlying sexual activity promoting vaginal patency.
- Sensitive issues skew participant representation and limit recruitment, and the results may not necessarily be applicable to the general population.
- Even with enthusiastic support and an intensive psychoeducational intervention, dilation rates were only marginally increased compared to standard care and this was only seen in younger women.
- There is no globally useful, validated tool for measuring the harm inflicted by encouraging dilation.
- Sexual function questionnaires are affected, if a woman's sexual drive is altered by her cancer.
- The outcome that matters to some women is sexual function and this is difficult to quantify in a meaningful, translatable, continuous variable.
- Vaginal length can be measured, but may bear no relationship to sexual well-being (Schimpf 2010; Weber 1995) or quality of life.
- Prophylactic and therapeutic dilation therapy needs to be considered separately and research is needed to determine when dilation therapy should start.
- Sample size calculations show that any randomised controlled trial with any meaningful robust outcome would be need to involve multiple centres and countries.

It is important to evaluate the effectiveness of a treatment that is recommended to many women when it may be of limited value, uses valuable nursing and radiographer time and may cause trauma and distress. This will require the development of a validated methodology to assess vaginal function and sexual well-being and large-scale, good-quality clinical studies, measuring validated outcomes that matter to women, not just those that are easy to measure.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Bahng 2012	Good-quality observational study but the only conclusion it can make is that women with stenosis have a lower probability of adhering to the dilation programme. This is not proof that prophylactic dilation is protective
Bruner 1993	There are no data provided for any measure of vaginal or sexual function and no data were available from the authors

Study	Reason for exclusion
Decruze 1999	This comparative study used historical controls that were not perfectly matched and the care in the control group was not defined, but it seems that some form of dilation therapy was available
Gondi 2012	Good-quality observational study but the only conclusion it can make is that women with stenosis have a lower probability of adhering to the dilation programme. This is suggestive but not proof that prophylactic dilation is protective
Jeffries 2006	Did not meet the inclusion criteria. This trial assessed the number of women who could be encouraged to dilate if they were offered intensive psychoeducational support
Law 2013	Good-quality observational study but the only conclusion it can make is that women with stenosis have a lower probability of adhering to the dilation programme. This is not proof that prophylactic dilation is protective
Miles 2012a	This RCT compared static with vibrating dilators, not dilators versus no additional treatment
Miles 2012b	This small observational study does not test the efficacy of dilation therapy
Poma 1980	This is a case series of 5 selected cases treated many years after cancer therapy
Robinson 1999	Did not meet the inclusion criteria, flawed methodology and prone to bias
Sobotkowski 2006	This is a good comparative study but the focus is on the application of mitomycin with a speculum. Whilst it is reasonable to assume that the treatment group had 2 additional examinations with a speculum that must have stretched the vagina, the absence of any difference in the groups could be due to numerous factors including the possibility that both groups were receiving some form of dilation care from another source
Velaskar 2007	Case series with unblinded measurements, the measuring tool is not disclosed and altered vaginal length might represent a different tolerance to being measured due to experience, rather than changes in anatomy

RCT: randomised controlled trial

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

Bruner 2011

Trial name or title	Randomized feasibility study of dilator use and an educational program
Methods	This pilot study will provide preliminary data on the feasibility a large trial of vaginal dilation. The aim is to test a method to increase compliance with the intervention. This study may also help inform sample size calculations for a larger randomised trial of the use of vaginal dilators to maintain vaginal length after VBT. It is hoped that the findings of the proposed study would provide the groundwork for future research that could have clinical implications for behavioural and device interventions to maintain sexual health after cancer therapy
Participants	Women with endometrial cancer treated with vaginal brachytherapy
Interventions	Women are randomly allocated different training and motivation in the use of dilators
Outcomes	Compliance with therapy
Starting date	December 2010, end date April 2013

Bruner 2011 *(Continued)*

Contact information	Debra Bruner, University of Pennsylvania School of Nursing, Room 330 Fagin Hall, 418 Curie Blvd. Philadelphia, Pennsylvania 19104-4217, USA. Tel: +(215) 746-2356; email: wbruner@nursing.upenn.edu
Notes	This is similar to the RCT by Jeffries 2006 and NCI UP 10G01

NCI UP 10G01

Trial name or title	Randomized Feasibility Study of Dilator Use and an Educational Program to Increase Compliance after Vaginal Brachytherapy for Endometrial Cancer
Methods	The purpose of this study is to see if the use of a vaginal dilator will help keep the vagina a normal length after vaginal brachytherapy for the treatment of endometrial cancer
Participants	Participants must have stage I-IIIc endometrioid endometrial cancer and have undergone a hysterectomy and oophorectomy +/- lymphadenectomy, have a planned postoperative vaginal brachytherapy and have no prior history of pelvic radiotherapy or chemotherapy
Interventions	Study participants will be randomised to 1 of 2 treatment groups. Participants in both groups will use the vaginal dilator. One of the groups will also spend time with a study nurse who will provide enhanced education about the device. From the beginning of the study and for the duration (6 months) all participants will be given instructions on when and how to use the vaginal dilator. Participants will be asked to continue dilator use for the entire 6 months and to keep a calendar tracking dilator use and any sexual activity. The calendars will be collected at 6 weeks and 6 months after beginning the study
Outcomes	During office visits questionnaires will be completed by participants and vaginal length will be measured by the doctor using a vaginal sound
Starting date	November 2008
Contact information	Peggy Gilbertsen, Clinical Trials Recruitment Nurse. Robert H Lurie Comprehensive Cancer Center. cancertrials@northwestern.edu; Tel: +01 3126951102 (the website updated in April 2014 describes Sara Duffey, Clinical Research and Education Specialist as the contact)
Notes	This is similar to the RCT by Jeffries 2006 and Bruner 2011

RCT: randomised controlled trial
VBT: vaginal brachytherapy

ADDITIONAL TABLES

Table 1. Description of studies containing data on vaginal dilation following radiotherapy

Author/date	Methodology and results *Limitations of the study*	Outcome measure
Poma 1980	**Case report** This report described 5 women who developed radiation stenosis. They had not subsequently had vaginal penetration since their radiotherapy and they were offered dilation therapy. They were parous, aged between 47 and 55 and their radiotherapy had been between 3 and 9 years previously (5 cases at 8, 8, 9, 3 and 9 years). Women were taught	Vaginal length after treatment

Table 1. Description of studies containing data on vaginal dilation following radiotherapy *(Continued)*

	to digitally massage their vagina with an oestrogen cream (2 g) twice a day until vaginal depth became evident. This demonstrated a possible effect from late dilation in these selected cases.	
Bruner 1993	**Cohort study** 90 women treated with intra-cavity radiation implants with or without external beam radiotherapy, with or without radical or total abdominal hysterectomy for either cervical or uterine carcinomas (stages 1 to 3) consecutively from 1989 to 1992 were recruited. Vaginal length was measured before treatment, and then 6 to 12 months, 12 to 24 months and more than 24 months after radiotherapy. This study measured vaginal length longitudinally correlated with type of treatment. Dilation and coital frequency was noted but not reported and authors (so far) have been unable to provide these data. However, they did show that measured vaginal length decreases with time despite adherence to the dilation therapy programme in 68% of women. Unlike the work by Velaskar 2007, Bruner 1993 showed the mean length was about a centimetre shorter a year after radiotherapy despite dilation use. The study showed a correlation between vaginal shortening and type of treatment and persistent vaginal shortening with time. It does not provide data linking coital frequency to ultimate vaginal length.	Vaginal length measured at pre-treatment, 6,12, 24 and beyond 24 months
Robinson 1999	**Randomised trial** The authors recruited 32 women with stage 1 or 2 cervical or endometrial carcinoma who were treated with radiotherapy. The control arm had a clinical consultation and literature containing information on normal sexual responses, vaginal dryness, the use of lubricants, Kegel exercises, vaginal dilators and alternative positions for coitus with instruction to dilate the vagina after treatment. The interventional arm also had a clinical consultation with instruction to dilate the vagina after treatment plus 2 separate 1.5-hour education sessions guided by information motivation behavioural skills model (informing women how to use dilators, motivating them to use them and teaching them how to use them). Women were randomised based on a random number table. This RCT showed that it is possible to encourage and support women successfully to dilate their vagina. A regression analysis demonstrated that the intervention was associated with greater compliance but this was only observed in younger women. In the younger age group (less than 41.5 median age of the population), 5.6% in the control group complied compared to 44% in the intervention group. In the older group compliance was 55.6% in the control group versus 48% in the intervention group. This demonstrates that the younger women did comply and therefore randomisation has succeeded in creating 2 distinct groups, one who rarely dilated and one that complied with instructions to dilate. Mean sexual healthy scores (SD) were the same in the 2 groups. The sexual health score in the experimental group was 0.401 (0.081) compared to 0.513 (0.126) in the group who rarely dilated (control group). This was independent of age. The RCT showed that the intervention increased dilation practice in a small post analysis subgroup but did not improve the sexual function score. *The timing of sexual health scores is not defined and the analysis subdivided data into the groups from older and younger women after it had been collected. The original paper may have been edited for brevity and did not describe how participants were randomly allocated or how contamination was minimised but the study lead author confirms that appropriate techniques were applied (personal communication) and there were no incomplete data sets. Although we have a comparison of sexual health scores in women who rarely dilated compared to a group who were more likely to dilate, sexual function was not the authors' primary outcome in this study. The sample size was small and over half of the intervention group still failed to comply with the protocol. In addition, this is not a trial where the outcome is measured vaginal length. However, sexual health scores were not the primary hypothesis and the intervention only made a small difference to the groups, meaning that there may have been a difference but the study design failed to detect it.*	Global sexual health scores Knowledge about sexuality, cancer and vaginal dilation compliance
Decruze 1999	**Unmatched, unblinded, uncontrolled case series with historical controls**	Clinical assessment of stenosis

Table 1. Description of studies containing data on vaginal dilation following radiotherapy *(Continued)*

	A retrospective review of stenosis 1 year after radiotherapy in women who had used the authors' own design of vaginal stent was compared to an uncontrolled group who never used a vaginal stent. Dilation began after completion of all treatment including intracavity radiotherapy. 70 women treated by either external beam radiotherapy, vaginal caesium only or combination of intrauterine vaginal caesium and external beam radiotherapy were recruited. There were 35 women in each group. 20 had stenosis who did not use a stent compared to 4 who had stenosis who did use a stent. The 4 that did use a stent who had stenosis were noteworthy because 1 was too frightened to use, 1 was confused and 2 did not understand how to use it. Once these 4 women had been encouraged to use it properly the authors say that the stenosis improved but no further details were given. An undefined clinical assessment of stenosis 1 year after radiotherapy was recorded in 35 women who used a stent designed by the study authors compared to 35 historical controls. 20 historical controls who did not use the same stent had stenosis compared to 4 who did. The 4 that did use a stent who had stenosis were noteworthy because 1 was too frightened to use it, 1 was confused, and 2 did not understand how to use it. Once these 4 women had been encouraged to use it properly the authors reported that stenosis improved, however no further details were given. *The report is valuable but limited because the study is not blinded and the control groups are not comparable. They state that their stent made a significant difference to the stenosis rate but stenosis was assessed by the authors who knew that their design of stent had been used. There was no record describing how these women were selected or why they were selected. Bias is compounded because there is a difference in the comparative groups in age, tumour site and type of radiotherapy. Those having no stent were on average 5 years older. Allocation was not concealed from the assessors and neither assessors nor patients were blinded to the technique. Therefore the risk of bias is high. This report is useful but does not meet the criteria to be included in any evidence-based review.*	at 1 year after radiotherapy
Jeffries 2006	**Randomised trial** The Jeffries 2006 RCT of psychoeducational intervention was designed to test the effect of increased compliance with vaginal dilation. The information-motivation-behavioural skills model of enhancing compliance with behavioural change was the basis for the intervention design. 42 sexually active women with cervical or endometrial cancer, who received pelvic radiotherapy, were randomised to either the experimental psychoeducational group or the information-only control group. Assessment via questionnaire occurred before treatment and at 6-week and 6-, 12-, 18- and 24-month follow-up. Assessment via interview also occurred at 6-, 12-, 18- and 24-month follow-up. These data support the strategy that investing in health resources to support women during this phase of their cancer journey does change the uptake of the prescribed therapy but provides no data on the effectiveness of dilation therapy.	No physical or vaginal symptom measurements were described
Sobotkowski 2006	**Non-randomised comparison** This study compared vaginal length in 31 women with advanced cervix cancer treated by radiotherapy and brachytherapy. 16 women were chosen to have mitomycin applied topically to the top of the vagina. Application of the drug took place 2 and 4 weeks after completion of radiotherapy by the use of a dry speculum and the application of a mitomycin soaked gauze placed in the vaginal vault for about 4 minutes. Vaginal length was measured before and after treatment. Women who received mitomycin applied to the top of the vagina with a speculum were compared with a non-specified group who did not. Vaginal length was not different after treatment (mean length of the study group (N = 16) of 6.5 cm +/- 2.02 and the control group (N = 15) mean 5.67 +/- 3.04. There were 4 vaginal occlusions in the control group and 1 in the study group. There were 4 vaginal wall synechiae in the control group and 2 in the study group. The authors concluded that the mitomycin applied by speculum made no difference to vaginal length *The authors do not describe how the cases were selected, the observers and the participants were not blinded to treatment and it was not a randomised study*	Vaginal length, vaginal occlusion and vaginal vault wall synechiae

Table 1. Description of studies containing data on vaginal dilation following radiotherapy *(Continued)*

Velaskar 2007	**Case series with longitudinal follow-up** Case series describing 89 of 100 women with stage 3 cervix cancer treated by radiotherapy; 45 also had concomitant chemotherapy. The median vaginal length was 6 cm 6 to 10 weeks after treatment. It was 9 cm 4 months later following the introduction of dilation practice. No further significant vaginal length was achieved with continued dilation 4 and 8 months later (median length was 10 cm at these assessments). Women tolerated a 6 cm measurer on the first vaginal assessment after radiotherapy and tolerated a larger one after 4 months of dilation experience. The main limitation of these data is that there is no control group to determine outcomes if dilation had not been suggested and we do not know if the reason women accepted a larger dilator in their vagina many months after the treatment was tolerance, familiarity or the resolution of inflammatory radiation oedema. *The authors do not describe how the cases were selected, how the measurements were taken, the observers and the participants were not blinded to treatment and readers are left wondering if the change in length is just a measurement artefact. It is possible that women tolerated greater penetration depth with experience and exposure to measurement and exposure to a foreign body in the vagina. The most important bias is the lack of a control group. However, the authors present convincing data to show vaginal lengthening following dilation but this is the opposite of the findings by Bruner 1993.*	Vaginal length measured before and after a programme of dilation therapy
Miles 2012a	**Randomised trial** This was a randomised trial of 61 women who had had radiotherapy for either advanced uterine or cervix cancer. Women were randomly allocated a static or vibrating dilator used during and for 3 months after radiotherapy. Qualitative and quantitative data on symptoms, sexual function scores and LENTSOMA scores before, during and 3 months after radiotherapy were collected and vaginal length, elasticity and tissue turgor before, during and after treatment were made with a tool that measured vaginal length from the vault to a vulval plate when a spring loaded force stretched the vagina. Elastic recoil was measured as the force on the inserted decreases from 10 to 8 Newtons. Women with cervix cancer had a shorter vagina than those who had uterine cancer and the elasticity was greater in younger women. However, dilation practice made no difference to vaginal length or elasticity (mean (SD) length (mm) and elasticity (mm/N) for women who did and did not dilate respectively; 76 (19) versus 74 (24) and 5.0 (3.9) versus 5.0 (2.2). There was no correlation with the duration of dilation after therapy with vaginal length or elasticity. Despite 61 evaluable cases, it was only possible to collect the full paired data set from 13. There was no detectable difference between the groups in change in vaginal elasticity, length, viscosity, LENTSOMA or sexual health scores at any time of the study. *The study was underpowered and recruitment was low suggesting a high risk of recruitment bias (a study that recruited women who may not represent the normal population).*	Change in vaginal elasticity, length, viscosity, LENTSOMA or sexual health scores from the beginning to mid and after radiotherapy and 3 months afterwards
Miles 2012b	**Tests of association** This observational non-interventional study was designed to study 60 women but only managed to recruit 21. Data were collected in a research clinic on dilation practice, coitus, smoking, past surgery and other therapies and correlated with vaginal measurements. Dilation had been encouraged during and after radiotherapy in this patient group. It was intended to see whether stenosis was reduced by dilation practice or if stenosis simply predicted women who had given up dilating because of their stenosis. The outcomes were vaginal length and elasticity. If the group who dilated frequently had different vaginal physiology then this strengthens the case that dilation causes less stenosis. *The study found no difference. This could be because the sample size was inadequate to detect a true difference or because dilation does not alter vaginal physiology.*	Vaginal elasticity and length in women who practise dilation after radiotherapy and those who did not
Gondi 2012	**Tests of association** This observational study recruited women with locally advanced cervical cancer treated with curative intent at a single institution with radiotherapy alone or concomitant	CTCAE version 4.0 score at 3 years after radiotherapy

Table 1. Description of studies containing data on vaginal dilation following radiotherapy *(Continued)*

	chemoradiotherapy. The association between stenosis (defined as grade ≥ 3 vaginal toxicity using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) occurring ≥ 6 months from treatment completion for cervix cancer and predating any salvage therapy) was compared to compliance with dilation (defined as poor moderate or high). High compliance was defined as following the protocol recommendations of vaginal penetration with either coitus or dilation twice a week for the first 2 years after treatment completion with at least monthly usage thereafter and no documented breaks in use. Poor compliance was penetration less frequently than monthly. Severe late toxicity rates were compared after adjusting for pertinent covariates. Compared to high dilator compliance, moderate (HR 3.6, 95% CI 2.0 to 6.5, P value < 0.001) and poor (HR 8.5, 95% CI 4.3 to 16.9, P value < 0.001) dilator compliance was associated with higher vaginal severe late toxicity. Other predictive factors for severe vaginal late toxicity included dilator compliance and age. The probability of vaginal severe late toxicity at 3 years after radiotherapy was also influenced by treatment (20.2% for radiotherapy alone and 35.1% for concomitant chemoradiotherapy; HR 3.0, 95% CI 1.7 to 5.2) and age > 50 (HR 1.8, 95% CI 1.1 to 3.0, P value = 0.013). This study shows that women who find it difficult to have vaginal sex or are difficult to examine vaginally have a lower rate of dilation use. The authors recognise that they are predicting that dilation frequency may be reduced because of pain or stricture, not necessarily because dilation and stretching skin improves the vagina. *The authors found that age > 50 is associated with a greater risk of stenosis. This is the opposite conclusion from the data in* Bahng 2012*.*	
Bahng 2012	**Tests of association** This retrospective review of 89 case notes of women with endometrial cancer treated by hysterectomy and brachytherapy (not external beam radiotherapy) tested the association of vaginal toxicity at various times with reported dilation frequency. Logistic regression multivariate analysis compared the association of retrospectively graded vaginal toxicity (NCI CTCAE v4.02) with age, active length and dilator use 2 to 3 times a week. Vaginal toxicity was defined as vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination. Increasing age, vaginal dilator use of at least 2 to 3 times a week, and shorter active length were found to be significantly associated with a decreased risk of vaginal stricture. The incidence of minor Grade 1 or asymptomatic vaginal toxicity was 33% and grade 2 to 3 symptomatic vaginal toxicity was 14%. Multivariate analysis of age, active length, and dilator use 2 to 3 times a week revealed odds ratios (OR) of 0.93 (P value = 0.013), 3.96 (P value = 0.008) and 0.17 (P value = 0.032) respectively. *The methodology is limited by the use of retrospective case note review and self reported use of dilation. The authors conclude that the association of dilation with less difficult coitus and examination is evidence that dilation is therapeutic. They do not comment on the possibility that the association is just a coincidental effect of pain or stricture inhibiting dilation practice. Also the study curiously reports less vaginal toxicity associated with increasing age and this conflicts with others including Gondi 2012. This is difficult to reconcile.*	Vaginal toxicities documented in case notes were converted retrospectively to CTCAE v4.02 grades.
Law 2013	**Tests of association** This correlation analysis examined the case notes from 109 women with cancer (rectal, N = 28; anal, N = 35; endometrial, N = 45; cervical, N = 1) and set out to measure a correlation between the size of the vagina 1 year after radiotherapy compared to its pretreatment size. Women had structured teaching to use dilators 3 time a week, regardless of sexual intercourse frequency and personal communication with the authors (2011) confirmed that dilation therapy began after the completion of radiotherapy. Self reported dilator size and vaginal symptoms were recorded in monthly diaries for a year. Vaginal stenosis was also assessed using CTCAE v3 score (NCI CTCAE v3) before and at 1, 6 and 12 months after radiotherapy. CTCAE v 3 defines grade 3 vaginal toxicity as surgically uncorrectable complete obliteration of the vaginal vault and there are no data on this outcome. The authors also reported whether the patient could insert the same dilator 12 months after treatment as she could before radiotherapy. Compliance (adherence/concordance)	Vaginal stenosis using CTCAE v3 (vaginal scaring sufficient to interfere with activity)

Table 1. Description of studies containing data on vaginal dilation following radiotherapy *(Continued)*

	to the dilation programme was measured as a percentage of time women said they used the dilator out of the number of times they were instructed (i.e. 3 times per week for a year; N = 156). Nonparametric analysis of variance showed that greater adherence to the dilation programme at 6 months was associated with a greater likelihood that the women could use the same size dilator at 12 months that she could before treatment. Other than confirming that P value < 0.05, no other data are available and, at the present time, are not yet available from the author. *These data have only been presented as a poster presentation and is impossible to know what other confounding variables affected the data. Anal cancer was particularly associated with less dilation and greater risk of stenosis, suggesting a risk of bias. It is possible that anal cancer predicts the radiotherapy type and dilation compliance, not that dilation use predicts (or causes) a return to the original vaginal size. The authors included coital frequency but this is not part of the analysis. The authors suggest that they were going to focus on CTCAE v3 toxicity but performed statistical analysis using the Fisher test (2 by 2 table) on the rate of self reported dilation use with the rate of self reporting of dilator size accommodated at 12 months compared to before treatment. The impressive statistical power (P value < 0.05) for such small numbers must mean a very large difference between the groups. However, this may not be the primary hypothesised outcome variable, multiple comparisons seem to have been made with no adjustment and no data other than a P value are available.* *Nevertheless, this is a preliminary report testing a prospective hypothesis with adherence to dilation and efficacy of vaginal dilation measured regularly. It seems that the authors convincingly show a strong association meaning that women who can fit the same dilator they used before treatment into their vagina at 12 months are also more likely to continue to use dilators. Likewise, women who could not achieve the original vaginal size could not insert the larger pretreatment size dilators into their vagina.*

CTCAE: Common Terminology Criteria for Adverse Events
HR: hazard ratio
LENTSOMA: late effects in normal tissues subjective, objective, management and analytic scale
RCT: randomised controlled trial
SD: standard deviation

Table 2. Direction of the effect of dilation according to when the study began dilation therapy

Study	Timing of dilation therapy	Direction of effect
Robinson 1999	During radiotherapy	No improvement detected
Sobotkowski 2006	During radiotherapy	No improvement detected
Miles 2012a	During radiotherapy	No improvement detected
Miles 2012b	During radiotherapy	No improvement detected
Poma 1980	After radiotherapy	Improvement in the vagina
Velaskar 2007	After radiotherapy	Improvement in the vagina
Gondi 2012	After radiotherapy	Improvement in the vagina
Bahng 2012	After radiotherapy	Improvement in the vagina
Law 2013	After radiotherapy	Improvement in the vagina

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Vagina explode all trees
#2 vagina*
#3 (#1 OR #2)
#4 MeSH descriptor Radiotherapy explode all trees
#5 Any MeSH descriptor with qualifier: RT
#6 Any MeSH descriptor with qualifier: RE
#7 radiotherap*
#8 radiation
#9 (#4 OR #5 OR #6 OR #7 OR #8)
#10 dilat*
#11 vibrator*
#12 device*
#13 lubricat*
#14 stent*
#15 cream*
#16 massage*
#17 stenos*
#18 fibros*
#19 scarring
#20 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (#3 AND #9 AND #20)

Appendix 2. MEDLINE search strategy

1 exp Vagina/
2 vagina*.mp.
3 1 or 2
4 exp Radiotherapy/
5 "radiotherapy".fs.
6 "radiation effects".fs.
7 radiotherap*.mp.
8 radiation.mp.
9 4 or 5 or 6 or 7 or 8
10 dilat*.mp.
11 vibrator*.mp.
12 device*.mp.
13 lubricat*.mp.
14 stent*.mp.
15 cream*.mp.
16 massage*.mp.
17 stenos*.mp.
18 fibros*.mp.
19 scarring.mp.
20 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 3 and 9 and 20

key:
mp = title, original title, abstract, name of substance word, subject heading word
fs = floating subheading

Appendix 3. EMBASE search strategy

1 exp Vagina/
2 vagina*.mp.
3 1 or 2
4 exp Radiotherapy/
5 radiotherap*.mp.

6 radiation.mp.
7 4 or 5 or 6
8 dilat*.mp.
9 vibrator*.mp.
10 device*.mp.
11 lubricat*.mp.
12 stent*.mp.
13 cream*.mp.
14 massage*.mp.
15 stenos*.mp.
16 fibros*.mp.
17 scarring.mp.
18 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 3 and 7 and 18

key:
mp = title, original title, abstract, name of substance word, subject heading word
fs = floating subheading

Appendix 4. RCTs: Jeffries 2006, Robinson 1999 and Miles 2012

Jeffries 2006

Methods	RCT
Participants	42 sexually active women, 21 to 65 years of age, diagnosed with Stages Ic to III cervical or endometrial cancer, who received pelvic radiotherapy. There were 23 (49%) women with stage I disease, 16 (34%) with stage II and 8 (17%) with stage III disease. The mean age of women in the trial was 43 years (SD = 10.3 years, range: 21 to 65). 2 (4%) women had a marital status of single, 31 (66%) were married, 3 (6.5%) were divorced and 11 (19%) women had common law as their status. There were 13 (28%) women educated to high school level, 21 (45%) women had a secondary education and 13 (28%) women had at least an undergraduate degree. 38 (81%) women were diagnosed with cervical cancer and 9 (19%) women had endometrial carcinoma.
Interventions	Intervention: psychoeducational intervention specifically designed to increase compliance with vaginal dilation Comparison: information-only control group Dilation began in the last week of therapy
Outcomes	Assessment of vaginal dilation compliance was made by questionnaire before treatment and at 6-week, 6-month, 12-month, 18-month and 24-month follow-up. Assessment via interview also occurred at 6-month, 12-month, 18-month and 24-month follow-up. No data are available on vaginal or sexual function.
Notes	This randomised trial is from the same group as the one led by John Robinson. It focused on compliance with treatment and no data on sexual scores were collected. The data are heterogeneous and the likely cause of the heterogeneity is the difference in ages.

Risk of bias table

Item	Judgement	Description

(Continued)

Adequate sequence generation?	Yes	Direct communication from one of the authors (JR) confirms that the block randomisation protocol was constructed using random number tables generated by Microsoft Excel Version 6.0. The block randomisation protocol was designed to randomly assign approximately equal numbers of groups of women to either the control or experimental interventions for both centres.
Allocation concealment?	Yes	As the author both designed the random assignment protocol and was the recruiter for the Calgary arm of the trial. Special precautions were undertaken to ensure she was blind to the assignment. First, the random assignment was based on relatively large blocks so that the next random assignment could not be predicted from the previous assignments. Second, the random assignment protocol was designed very early in the experimental design to minimise the chance that she would remember the assignment order. Each assignment was then sealed into numbered envelopes that were not opened until the small groups of women were accrued. Sealed assignment envelopes were also supplied to the research assistant in Edmonton.
Blinding?	No	The control group knew they were not receiving additional psychoeducational support
Incomplete outcome data addressed?	Yes	100% of women analysed: 47/47
Free of selective reporting?	Yes	There is no suggestion of selective reporting
Free of other bias?	Yes	This was a well-conducted trial given the potentials for bias

Robinson 1999

Methods	Random allocation was directed by a random number table concealed in sealed opaque envelope
Participants	32 women with stage I or II cervical or endometrial cancer treated with radiotherapy. 24 (75%) women were diagnosed with stage I/II cervical carcinoma and 8 (25%) women had endometrial carcinoma. Radiotherapy was the sole treatment in 9 (28%) women; the other 23 (72%) had a combination of radiotherapy with surgery and/or chemotherapy. 20 women (63%) were taking hormone replacement therapy. The mean age of women in the trial was 46.5 years (range = 28 to 73 years). There were 3 (9%) women with an education grade 1 to 8, 11 (34%) women with grade 9 to 12 and 18 (56%) women had at least some post-secondary education.
Interventions	**Intervention:** psychoeducational programme using an information-motivation-behavioural skills' model to influence compliance Women randomised to the experimental intervention arm attended two 1.5-hour psychoeducational group sessions co-facilitated by the lead and last author using the information-motivation-behavioural skills model described by Fisher 1996. Information about sexuality in general and sexuality and cancer was presented using a variety of teaching aids and techniques: a three-dimensional (3D) model of the female pelvis was utilised; women were shown and able to feel different kinds of vaginal lubricants; explicit instruction for vaginal dilation was given; and the women were shown and able to handle a vibrator. In addition to receiving a copy of Sexuality and Cancer (Schover 1988), the participants were given a handout on the additional material covered in the meetings. The motivational component of the intervention was designed to enhance the women's view of their sexuality and to promote the idea that sex can be pleasurable despite cancer treatment. The group format allowed for social comparisons, normalisation of feelings, and social connections. For example, the women were encouraged to go together to "sexuality" shops to pur-

(Continued)

	chase vibrators and lubricants. They were encouraged to discuss their experience and fears. Issues such as changes in body image and fears about painful intercourse and vaginal bleeding were raised by the facilitators if they were not raised by the women. The behavioural skills component focused on teaching women how to effectively use dilators and lubricants, and Kegel exercises **Comparison:** standard care Women in the control arm met with a counsellor and were given a copy of Sexuality and Cancer: For the Women Who Has Cancer, and her partner (Schover 1988). This booklet provides a very frank description of both the "normal" sexual response and sex-related consequences of cancer and its treatments. It covers topics such as vaginal dryness and the use of lubricants; painful intercourse and strategies for managing this problem, such as Kegel exercises, vaginal dilators and alternative positions for intercourse; managing anxiety; and changes in body image. During the counselling session, women's questions about cancer and sexuality were answered by referring to the appropriate sections of the booklet. The attention of all women was drawn to the sections of the booklet related to dilation and the use of lubricants.
Outcomes	Global sexual health, knowledge about sexuality and cancer, fears about sexuality after cancer and vaginal dilation compliance. No attempt was made to measure vaginal anatomy.
Notes	—

Risk of bias table

Item	Judgement	Description
Adequate sequence generation?	Yes	Randomisation involved a random number table
Allocation concealment?	Yes	Direct communication from the first author confirms that random allocation was directed by a random number table concealed in sealed, opaque envelopes
Blinding?	Unclear	It would have been impossible to conceal the group allocation from participants. It was unclear whether the outcome assessor was blinded.
Incomplete outcome data addressed?	Yes	When the authors began to analyse the data, they became aware that 8 of the 40 participants recruited to the study had dropped out after randomisation. These data were excluded in the analysis (20% of women analysed: 32/40). This means that the analysis did not use the intention-to-treat principle.
Free of selective reporting?	Yes	An honest critique of the limitations of the data and the wiliness to openly share the data impressed us to conclude that the paper was not selectively reported
Free of other bias?	No	The authors claim that the intervention increased compliance in the young but critical review of the paper makes it difficult to assess this conclusion. Data are available from 1 in 5 young women aged below the median age who continued dilating at the 3-month assessment compared to 3 in 4 who were given encouragement. However, there were 14 subjects in the control group and 18 who were allocated the intervention so data should have been available in 7 and 9 cases respectively under the median age. Also, the authors gave data on the number of responses to questioning about compliance and their table includes 36 responses in the control group out of 18 cases but 45 responses out of 14 women. It is likely that the scores for the same women have been repeated

(Continued)

	and this requires a prior hypothesis and more complex statistical modelling, taking the analysis of variance and repeated measures into account.

Footnotes

Miles 2012

Allocation	Static dilator	Vibrating dilator
Number with complete data	7	6
Nulliparous:multiparous	4:3	3:3
Cervix:endometrial cancer ratio	4:3	5:1
Age: median; mean (SD)	45; 50 (15)	46.5; 46 (9)
Had current sexual male partner:no current sexual partner	4:3	4:2
EORTC QoL score before treatment (median)	65	57.7
Sexual function SVQ score (mean (SD) intimacy domain) before treatment	14 (8.3)	15 (7)
Sexual function SVQ score (mean (SD) self image domain) before treatment	8 (3.3)	9 (2.0)
Sexual function SVQ score (mean (SD) sexual interest domain)	8 (4.7)	10 (3.1)
LENT SOMA score before treatment (median)	4	0
Vaginal length at 5N before treatment (mean; SD)	90 (34)	88 (46)
Vaginal length at 8N before treatment (mean; SD)	107 (16)	104 (17)
Vaginal length at 10N before treatment (mean; SD)	108 (17)	106 (16)
Vaginal elasticity 5-8N before treatment (mean; SD)	6 (13)	5.5 (11)
Vaginal elasticity 8-10N before treatment (mean; SD)	1 (0.80	1 (1.7)
Vaginal viscosity score before treatment at 8N (mean; SD)	20 (29)	7 (13)

WHAT'S NEW

Date	Event	Description
17 July 2018	Amended	Next stage expected date amended.
4 July 2018	Review declared as stable	Unlikely that studies in this topic area will change the conclusions.

HISTORY

Protocol first published: Issue 3, 2008
Review first published: Issue 9, 2010

Date	Event	Description
7 May 2014	New citation required but conclusions have not changed	We identified no studies for inclusion. However, we found four studies that did not meet the inclusion criteria but merited discussion. We added one ongoing study.
7 May 2014	New search has been performed	This work updates the 2010 review.

CONTRIBUTIONS OF AUTHORS

TPM: original idea; NJ and TPM: analysis; NJ and TPM: writing protocol and review.

DECLARATIONS OF INTEREST

TPM and NJ have an academic research grant from the Royal United Hospital NHS Trust to correlate vaginal dilator use with vaginal anatomy. The findings of this review helped inform the trial rationale and design. The lead author has received educational grants, equipment for research and a travel grant to attend the IGCS in Santa Monica in 2007, IGCS meeting subgroup in Prague 2010 and ASTRO meeting in Miami 2011 from Owen Mumford, manufacturers of Amielle 2010. The lead author is also the president of the National Forum of Gynaecology Oncology Nurses and Owen Mumford and MDTI (dilator manufacturers) have been some of the outside agencies who have paid to attend the annual national scientific meetings. They have also supported the National Forum's journal and provided a grant to Health Care Education (Bristol) for lecturing and consultancy. Sh! of London provided equipment for a research project.

Both authors have written reviews, guidelines and scientific studies in the field of dilation therapy and the lead author is the chair of the international guidelines group and the Macmillan UK lead nurse for assessing the late effects of radiotherapy.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Health, UK NHS Cochrane Collaboration Programme Grant Scheme CPG-506, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol was designed with the expectation that data existed to support current practice and this review was expected to quantify the strength and magnitude of the effect from the intervention. The absence of data surprised the authors and we then expanded the search criteria to provide an exhaustive literature trawl. The initial protocol included a strategy for meta-analysis but data were not synthesised and heterogeneity was not explored because the comparisons were restricted to single trial analyses. The initial protocol intention was to identify trials and abstract data as recommended in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) by:

- author, year of publication and journal citation (including language);
- country;
- setting;
- inclusion and exclusion criteria;
- study methods (trial design, duration, setting, study inclusion criteria);
- study population;
  - total number enrolled;
  - patient characteristics;
  - age;
- cancer details at diagnosis;

- total number of intervention groups;
- type of dilator interventions;
- risk of bias in study (see below); and
- duration of follow-up.

We will extract data on outcomes as below:

- For dichotomous outcomes (e.g. psychosexual morbidity, vaginal stenosis) we intend to extract the number of patients in each group who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a relative risk (RR).
- For continuous outcomes (e.g. QoL, measure of sexual function), we intend to extract the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (if trials measured outcomes on the same scale) or standardised mean difference (if trials measured outcomes on different scales) between treatment arms and its standard error.

Where possible, the intention is to extract all data relevant to an intention-to-treat (ITT) analysis, in which participants are analysed according to their assignment groups, note the time points outcomes were collected and report and assess the risk of bias in included RCTs and excluded studies using The Cochrane Collaboration's tool and the criteria specified in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This includes assessment of:

- sequence generation;
- allocation concealment;
- blinding (of participants, healthcare providers and outcome assessors);
- incomplete outcome data;
- selective reporting of outcomes;
- other possible sources of bias using the 'Risk of bias' tool independently and with consultation;
- measures of the effect of treatment (for dichotomous outcomes, the RR; and for continuous outcomes, the mean difference between treatment arms);
- the proportion of participants in each intervention arm whose outcomes are not reported at the end of the study.

We will assess heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage of heterogeneity between trials that cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, if possible, by subgroup analyses (see below). If there is evidence of substantial heterogeneity, we will investigate and report the possible reasons for this. Pooled data meta-analyses will use the following methods.

- For time-to-event data, we will calculate pooled hazard ratios (HRs) using the generic inverse variance facility of RevMan 5 (RevMan 2014).
- For dichotomous outcomes, we will calculate the RR for each study and then pool these.
- For continuous outcomes, we will calculate pooled mean differences between the treatment arms at the end of follow-up if all trials measured the outcome on the same scale, otherwise we will calculate pooled standardised mean differences.

NOTES

An earlier version of this review was also available in the *British Journal of Obstetrics and Gynaecology* 2010 (Johnson 2010) and in Miles 2012c.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents [therapeutic use]; Benzydamine [therapeutic use]; Brachytherapy [adverse effects]; Constriction, Pathologic [etiology] [therapy]; Dilatation [adverse effects] [*instrumentation]; Estrogens [therapeutic use]; Hyperbaric Oxygenation; Pelvis; Radiation Injuries [*therapy]; Radiotherapy [adverse effects] [methods]; Rupture [etiology]; Sexual Dysfunction, Physiological [etiology] [*therapy]; Time Factors; Vagina [injuries] [pathology] [*radiation effects] [surgery]

MeSH check words

Female; Humans