Sexual function in cervical cancer patients after radiation therapy

A systematic review

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Abstract

Objective: Cervical cancer (CC) has a low mean age world-wide, and it is today a known fact that many of these women undergoing a number of different treatment modalities including radiotherapy for their disease may develop a decreased sexual health. The purpose of this systematic review was to asses the effect of radiotherapy on sexual function in women treated with radiotherapy for their cervical cancer.

Methods: A systematic review was performed on English-language articles dated from 1993 and the search was performed until august 2012. Searches identified and included both cross-sectional and cohort studies though MEDLINE, EMBASE, CINAHL and SveMEd+ databases. Methodological quality where assessed using checklists recommended by The Norwegian Knowledge Centre for Health Services (NOKC). Meta-analysis' were performed using Review Manager 5.

Results: Nine observational studies with controls where eligible for the systematic review, with the total of 1635 participants. Meta-analysis showed that women treated with radiotherapy for their cervical cancer had a significant greater risk for developing dyspareunia (Relative Risk, RR, 4.37), narrow/short vagina (RR 5.99), vaginal dryness (RR 3.04) and decreased sexual interest (RR 1.43) compared to healthy controls. When comparing the same four outcome-measures with women treated with surgery only as a control group, only dyspareunia (RR 1.36) where found to be significantly higher compared to control.

Conclusions: Results from this review suggests that there is some evidence that radiotherapy could cause a decreased sexual functioning in women treated for cervical cancer. Further studies are needed in this field, because patients will more and more relate to health-care as a product and demand that late-effects and rehabilitations of these be put on the agenda. Sexuality will always be important on the subjective level and it would be beneficial to make use of better inquiry-models that involves both qualitative and quantitative scientific methods.

Sammendrag

Bakgrunn: Cervix cancer (CC) er en krefttype som har lav gjennomsnittsalder verden over, og det er kjent at mange av disse kvinnene, som gjennomgår et spektrum av behandlinger inkludert strålebehandling, kan få nedsatt seksuell helse. Hensikten med denne systematiske oversikten var å se på effekten av stråleterapi på seksuell funksjon hos kvinner som får strålebehandling mot sin cancer cervix.

Metode: En systematisk gjennomgang av engelskspråkelige artikler ble gjennomført. Artiklene var datert i fra 1993 og siste søk ble utført i august 2012. Både tverrsnittsstudier og kohorter ble inkludert i søkene som ble gjort i databasene MEDLINE, EMBASE, CINAHL og SveMEd+. Metodologisk kvalitet ble gransket med bruk av sjekklister utarbeidet og anbefalt av Kunnskapssenteret - Nasjonal kunnskapssenter for helsetjenesten. Metaanalyser ble utført ved bruk av Review Manager 5.

Resultat: Ni observasjonsstudier ble valgt ut til å være med i den systematiske oversikten, hvorav totalt 1635 informanter. Meta-analyser viste at kvinner som har fått strålebehandling hadde en signifikant større risiko for å utvikle smerter ved samleie (risk ratio, RR, 4.37), trang/kort vagina (RR 5.99), vaginal tørrhet (RR 3.04) og lavere seksuell interesse (RR 1.43) sammenlignet med friske kontroller. Sammenlignet med kvinner som kun var behandlet kirurgisk ble det funnet en signifikans (RR 1.36) for at kvinner som var behandlet med stråleterapi hadde økt risiko for å utvikle smerter ved samleie.

Konklusjon: Resultatene i fra denne studien viser at det er mulige årsakssammenhenger mellom strålebehandling og seksuelle dysfunksjoner, men det er også et faktum at det trengs flere og bedre studier rundt temaet kvinner seksuelle helse etter behandling for gynekologiske cancere. Ettersom tiden går vil pasienter stadig kreve mer av helsevesenet og kravet om å sette bivirkninger og seneffekter på agendaen har allerede blitt synlig. En større åpenhet om seksualitet og hvordan det best mulig kan rehabiliteres kommer alltid til å være viktig for individet og man kunne hatt nytte av å bruke kombinasjoner av kvalitative og kvantitative undersøkelsesmetoder i for å studere slike temaer.

Preface

As I work as a radiotherapist in one of the largest cancer centers in Northern Europe, I obviously wanted my master thesis to be about cancer patients. The stories and disease-stages of the cervical cancer patients I have met during my career have been diverse, but it has always made an impact on me how young many of these women are. Sexual health and functioning was a very small part of my previous education and as I began my career I quickly realized that the need for information about this topic was probably just as required amongst personnel as it was to patients.

Choosing a systematic review became the obvious choice of method for me as I went through heaps of literature early on in my project. Working with a systematic review has been a quite steep learning-curve, but none the less inspiring and very useful as I have learned a lot about doing research in methodology as well as cervical cancer and its challenges both for health personnel and the women living with this disease.

My supervisor during my work with this thesis has been senior researcher Lene Kristine Juvet at The Norwegian Knowledge Centre for Health Services. In addition I have had help from senior librarian Marie Isachsen at Oslo University Hospital Medical Library. Thank you both for your help, valuable comments and support.

I would also like to thank my employer, Oslo University Hospital and my superintendent Hildegunn Aase for making sure my work-schedule was in sync with my hours at university, and for giving me leave for exams and to finish my master-thesis. Finally, I would like to thank my family, friends and closest colleagues, (you know who you are), for supporting and cheering me on during the last three years of my master studies in Oslo.

Oslo, February 2013

Monika Poulin Hansen

Contents

1 Cervical Cancer

The incidence of cervical cancer is approximately 300 women yearly in Norway, and worldwide, this disease is rated as number two in cancer occurring in women [1]. Cervical cancer was for years the diagnosis that dominated gynecologic cancers. Since statistics have been collected at Kreftregisteret, the time-period of 1971-75 showed the highest incidence of cervical cancer with a number of 18 per 100000 per year (See Figure 1). Since the late eighties and early nineties, the curve for this diagnosis have decreased and almost deflated during the 2000's, probably because of Norwegian authorities' implementation of an organized screening-program [1, 2]. According to the Organisation for Economic Co-operation and Development, OECD, Norway has the highest five year relative survival rate in amongst the other OECD countries[3] (see Figure 2).

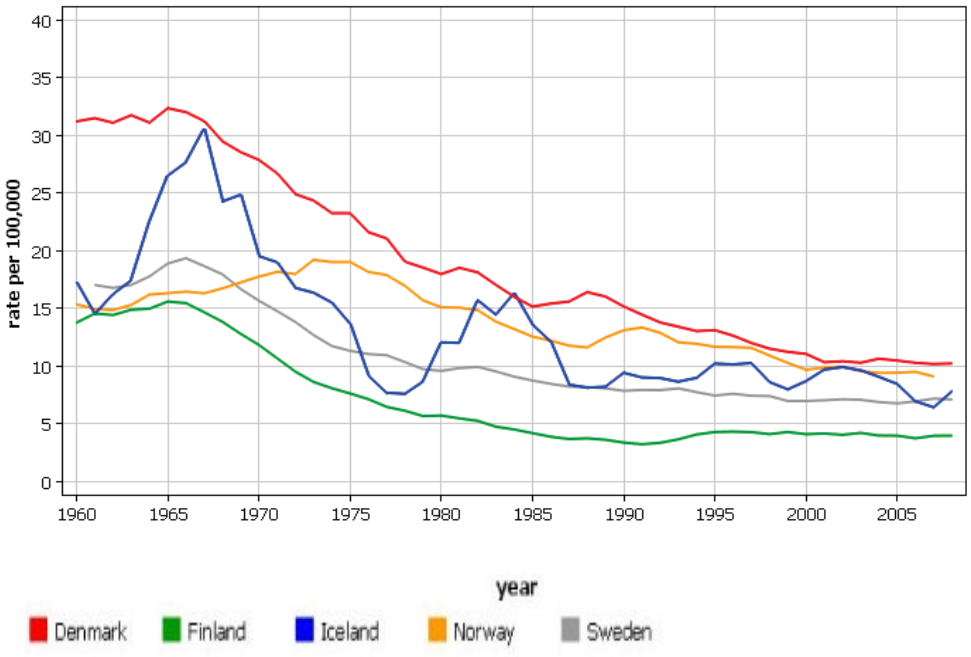


Figure 1: Age-standardized (world standard population) incidence of cervical cancer/105 in Denmark, Finland, Iceland, Norway and Sweden in 1945-2008[4].

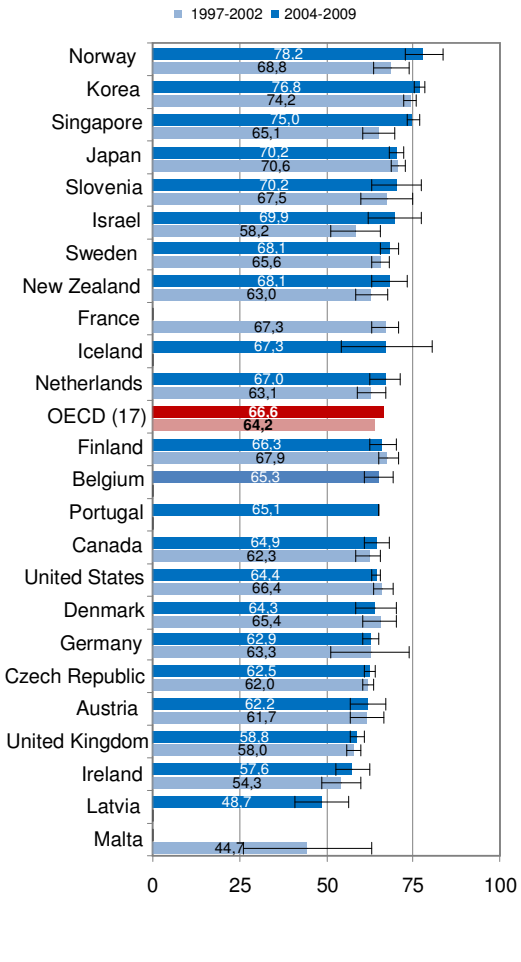


Figure 2: Cervical cancer five-year relative survival rate, 1997-2002 and 2004-2009 (or nearest period).[3]

Gynecologic cancers are divided into stadiums according to clinical, histological and radiologic findings. For cervical cancer, the work on classification and stadiums, started already in the 1920's at the request of the World Health Organization (WHO). Today, it is The International Federation of Gynecology and Obstetrics that continues this work, and the system of classifications used today are named after this federation (FIGO)[2].

1.1 Cervical intraepithelial neoplasia (CIN) and screening.

Precancerous stadium of cervical cancer is called cervical intraepithelial neoplasia (CIN), and can be divided into three different stadiums (see Figure 3). CIN is typically detected during routine screening, Papanicolaou test, so-called “Pap smear” (cytological screening). Screening of women for cervical cancer was first introduced in Finland in the early 70’s, and it was quickly decided that the findings of abnormal cell growth at an early stadium led to a reduced mortality rate. In Norway, organized screening started in 1995 with women between the ages of 25 and 70 getting called in every third year, so that it is possible to detect precancerous states. No randomized trials where conducted worldwide pre mass-screening of women. It is rather now, with the reduced mortality rates, that the value of screening can be seen[2].

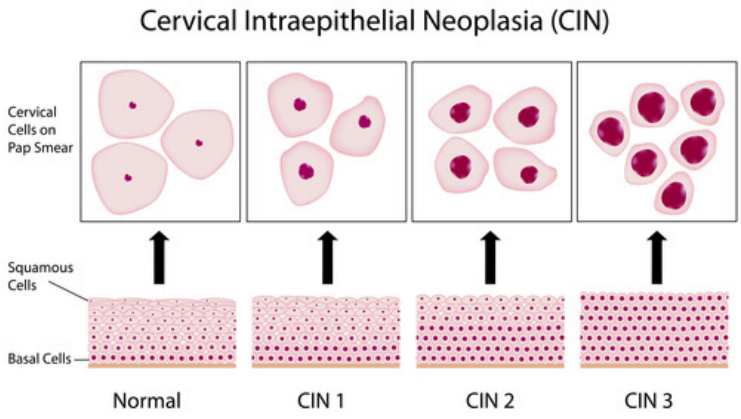


Figure 3: Stages of Cervical Intraepithelial Neoplasia (CIN)[5].

Every woman diagnosed with CIN1 in Norway, gets further follow-up with a colposcopy and biopsies. (A colposcopy is an electric microscope that can enhance areas of interest up to 25 times). Women diagnosed with CIN1 via a pap-smear very often experience that abnormal cells disappears by itself. It is rarely necessary to remove these cells on first time diagnosis. These women are instead followed up over a time period with examinations, since it is known that in some cases, “mild” CIN may develop into higher stadiums[2, 6].

Women diagnosed with CIN2 and CIN3 has what is called high grade stadiums of CIN and will need treatment, so that all risk of further developing cancer is removed. Cervical conization is an intervention where part of the cervix that is affected by the abnormal cell growth is removed. It is a fairly simple procedure where a loop, knife or laser is used, and it is normally just a small part of the cervical tissue removed so that the intervention does not in any case intervene with the woman's ability to get pregnant. The prognosis of these precancerous stages is very good, with a later risk of developing cancer less than 1 %. It is also possible to detect and further treat abnormalities that may have been left under the conization at a later follow-up[2, 6].

1.2 Development of cervical cancer

It has been known for a while that the risk of developing cervical cancer increases with the number of sexual partners, and early sexual debut. As early as the 1800's, it was discovered that married women had a greater chance of developing gynecologic cancer, than the nuns in the monastery[7]. From this, science was made to believe that sexually transmitted diseases could have an impact on developing the disease. It is today detected that certain types of the Human Papilloma Virus (HPV 16 and 18), could be oncogenic, and thereby contribute to the development of cervical cancer. Theses types of HPV create an inflammation of the cervical mucosa, which in most women will disappear in a matter of months. If the inflammation becomes chronic on the other hand, cells in the affected area might start to change and a neoplastic development may occur in the mucosa. Abnormal cells could develop into cancer cells, which again could grow into nearby tissues. Then again, it takes years to develop cancer, and most often these cells will end up in the stadium they are in or just go back to their normal state[2, 8].

Around 85 % of all cervical cancers derive from squamous epithelial cells in the area where the cervical canal meets part of the uterus, the transformation zone. (Insert picture here). Adenocarcinomas or also cancer from other types of cells in the cervix make out the last 15 %. An early stage, cervical cancer may be completely asymptomatic or give very few symptoms. When a women first seeks medical help due to symptoms it is most likely because of vaginal bleedings (intermenstrual, postcoital or contact), and also vaginal discharge. In

addition to this it may be an indication for advanced cervical cancer if the woman experiences anemia, pain, and weight-loss, loss of appetite or fatigue/tiredness[8].

1.2.1 Diagnostics and treatment for cervical cancer

Cervical cancer in Norway today is diagnosed after system and criteria before put into the FIGO classification system (Table 1). Defining the stage of disease in the patient is first done via a gynecologic examination where the patient is under anesthesia. The medical examiner will inspect the whole vagina in addition to determine if there is tumor infiltration to the nearby tissue by palpation of the area between the vagina and the rectum. A cystoscopy is also done to determine tumor infiltration to the bladder. An MRI scan is then being done of the whole pelvic and abdominal area to check for further tumor infiltration and possible spread of disease to the pelvic and para aortic lymph nodes. The MRI also reveals how the kidneys drainage is working. Lastly, a chest x-ray is done to determine if the disease has spread to the lungs[8].

Table 1: Shows staging in cervical cancer after the FIGO system. (FIGO 2009)[8]

Stage IA1	No visible tumor; microscopic invasion maximum 3 mm in depth and 7 mm on the surface of the epithelia (width).
Stage IA2	No visible tumor; microscopic invasion maximum 3-5 mm in depth and 7 mm on the surface of the epithelia (width).
Stage IB1	Clinically visible tumor limited to cervix or microscopic tumor greater than stage 1A; Largest diameter of tumor >4 cm
Stage IB2	Clinically visible tumor limited to cervix; Largest diameter of tumor≥ 4 cm
Stage IIA1	Tumor invasion beyond the cervix, into the upper part of the vaginal mucosa, no extension into the parametrial tissue. Tumor no greater than 4 cm in diameter
Stage IIA2	Tumor invasion beyond the cervix, into the upper part of the vaginal mucosa, no extension into the parametrial tissue. Tumor greater than 4 cm in diameter
Stage IIB	Tumor invasion into parametrial tissue, but not into the pelvic wall
Stage IIIA	Tumor invasion to the lower third of the vagina, but not into the pelvic wall
Stage IIIB	Tumor invasion onto the pelvic wall or hydronephrosis or nonfunctioning kidney
Stage IVA	Tumor invasion into the mucosa of the bladder or rectum
Stage IVB	Disease has metastasized to distant organs

When diagnosed with cervical cancer, the growing tumor is removed and any of the pelvic lymph nodes the disease might have spread to. Spread of disease to lymph nodes is often directly correlated to tumor size, but can also be influences by tumor location or tumor invasion of the blood and/or lymphatic system. For tumors in stages IAI, it should suffice to remove the lesion with either conization or surgical hysterectomy[9]. When it is pre-detected or detected during the surgical procedure that there is tumor infiltration to the blood or lymphatic system, lymph nodes in the pelvic wall are removed and sent to histological examinations to determine if the disease have spread and how far. It is today recommended to remove tumors in stages IA2 and IB in addition to smaller tumors in stage IIA, surgically through radical hysterectomy, where the whole uterus is removed with nearby tissue including the fallopian tubes, cervix and also usually the upper part of the vagina. The pelvic lymph nodes are also removed during the hysterectomy [7-10].

Cervical cancer has a low mean age for diagnosis, and surgical procedures in women in fertile age, with fairly small tumors are often modified so that it is possible to bear children[9]. It is chosen, if possible, to do a tracelectomy, a subtotal removal of the cervix in addition to remove only the most necessary parametrial tissue. Pelvic lymph nodes that have to be removed can be done so with a laprascopic intervention [6, 11].

Patients with large tumor growth and affected lymph nodes have greater chances of recurrence of disease. These are patients that today are treated with several modalities for their cancer, in form of adjuvant radiotherapy and chemotherapy[9]. Science shows that cytostatic treatment can make cancer cells more radiosensitive, so that it can reduce the chance of recurrence of disease, and may increase chances of survival for this group of patients [12-14].

Cervical cancer stages IIB to IVA get treated with radiotherapy as the standard treatment modality. Patients typically get an external radiation dose of 40-45 Gray (Gy) to the pelvic area and lymph nodes in addition to an extra dosage “boost” to the tumor area. Most of these women also go through intracavitary radiation, (brachy therapy), 5 to 7 times, as a supplement to the external therapy [15].

Curative patients having their medical treatment at Oslo University Hospital get adjuvant chemotherapy once a week for six weeks. This is done intravenously, but in small doses to

reinforce the radiation therapy. The exception for chemotherapy is if the patients have decreased kidney function or a reduced general condition [16, 17].

1.2.2. Ways to metastasize

It is possible for cervical cancers to grow out through the cervical wall and into the parametrial tissues around. The pelvic walls, the vagina, the bladder and the rectum can all be affected by the disease. In some cases fistulas occur into the bladder and/or the rectum because of the tumor infiltration into nearby tissues. It is normal that tumor cells can spread with the lymphatic system to lymph nodes in the pelvic area and also up the aorta, sometimes all the way up to the mediastinum and the supraclavicular area. It is also possible for tumor cells to spread via blood vessels to the lungs and the liver [8].

1.2.3 Prognosis

The prognosis for cervical cancer is like all other cancers, closely linked to the tumor extent at the time of diagnosis and treatment. Size of tumor, affection of lymph nodes and infiltration of parametrial tissue are all contributing factors to the extent of the disease. A low stage of disease is correlated with longer life expectancy for patients. The overall 5 year life expectancy for all stages of cervical cancer is today in Norway approximately 77 % as seen in Table 2 [1, 2, 7, 8].

Total	76.8 %
I	93.1 %
II	73.0 %
III	44.9 %
IV	18.0 %
Unknown	73.8 %

Table 2: 5 year relative survival in percent after localisation, stage. Time of diagnosis here: 2005-2009[1]

2 Tumor-biology

All bodily tissues are dependent on the fact that cells divide and renew themselves in the right kind of tempo. This is crucial for the organism to work as it should. An easy definition of cancer is abnormal cell growth/division also called profilation. Abnormal cell-growth could derive from any cell in the body, and turn into a malignant growth. Malignant tumors are characterized with the fact that they consist of cells with a rapid profilation, and that they grow into and destroy nearby tissues. These tumors also get a certain look, when they easily "branch out" like claws into parametrial tissue. This is how the disease got its name "cancer", from the Latin verb for crab. As opposed to normal tissue, malignant tissue consists of a heterogenic group of cells when it comes to size and shape. Even though the malignant tumor have derived from one type of cells, it is possible that other parts of the population may consist of other types of cells [18].

2.1 Proto-Oncogenes and Tumor Suppressor genes

A proto-oncogene could be any gene in the organism that mutates into an active oncogen and thereby contributes to cancer development. Oncogenes work by stimulating cell-growth and cell-division within the organism. In addition to this, some types of oncogenes are programmed to inhibit the cells natural self-destruction, apoptosis, in cases where it is necessary for the cell to self-destruct because of serious mutations occurred during the cell-cycle. Between 100 and 200 proto-oncogenes are known today [2].

A tumor suppressor gene can be viewed as the opposite of a proto-oncogene. The tumor suppressor gene P53 is especially important to the human cell-cycle. If the gene detects damage to the DNA-molecule that is to be replicated during the S-phase of the cell-cycle, it has the ability to delay time for the DNA-replication and create extra time in the cell-cycle to repair any damages. If the damage found is too great to repair, the P53 gene is to stimulate the cell to apoptosis or self-destruction so that the cell does not transmit any mutations to the daughter-cells. The P53 gene is damaged or inactivated in a lot of cancer-cells, so that it is not

able to help repair damages, and mutated DNA is recreated. When developing malignant cancer, a vicious circle is created when oncogenes are activated and tumor suppressor genes are inactivated, so that the cell-profilation will continue to produce mutated cells [2, 18].

It is a known fact today that cervical cancer derive from precancerous stages, CIN, and that the virus HPV can initiate these pre-stages. A lot of todays research, (as well as decades behind us); have been interested in the HPV virus' role within tumor-genesis. In cervical cancers the HPV virus is likely to be integrated in the host-genome, and it looks like this can lead to coding for two new proteins, E6 and E7, both who are frequently detected in cancerous disease. E6 and E7 bind themselves to especially tumor suppressor genes P53 and Rb, and contribute to cell-changes, when both these tumor suppressor genes play important parts in the cells life-cycle. E6 binds to P53, as E7 binds to Rb, and leads to decreased function and destruction of the tumor suppressor genes and thereby also making it easier for oncogenes to obtain control over the cells development [2, 7].

Because only some women with HPV develop cancer, it is clear that there must be other oncogenes and tumor suppressor genes that contribute to this type of cancers etiology [7].

3 Radiation therapy for cervical cancer

Radiation therapy has been a way of treatment for cancer since the beginning of the twentieth century when we where first able to develop the radioactive isotope Radium for therapeutic treatments. Since then, this subject matter has been under a massive development related to physics, biology and technology, and today, radiation therapy is seen as the second best treatment for cancer next after surgery [19].

The indication for radiation treatment is that it is often used in areas of the body difficult to reach with surgery or where surgery increases the risk of disability and/or death. It is just like surgery a local treatment of very high precision. The treatment is based on physical laws on interaction between radiation and bodily tissues. Interactions between radiation and tissue can be seen as a transmission of energy. The energy transmitted to the tissue can be calculated into what we call absorbed dose and is measured in Gray (Gy). 1 Gy consists of 1 Joule absorbed energy per kilogram [19].

3.1 External radiation

Radiation therapy can be divided into external therapy and internal (brachy) therapy.

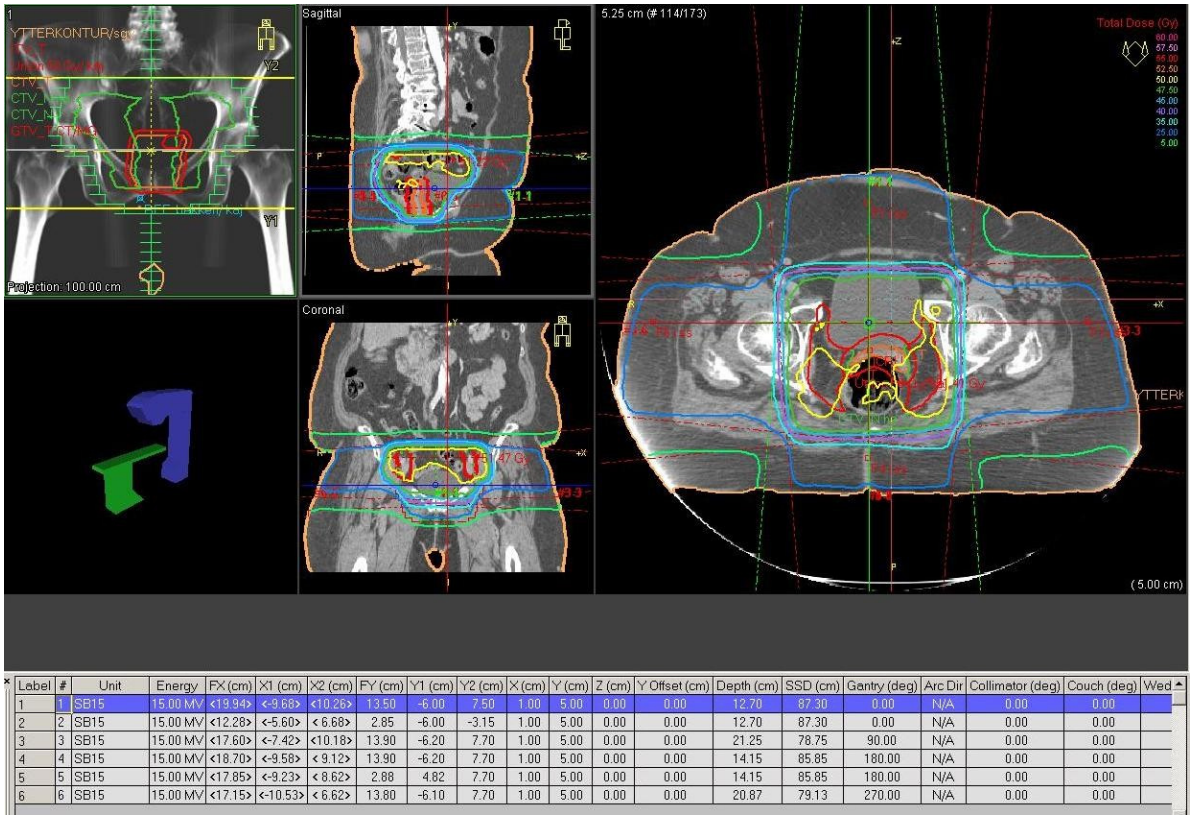
External therapy treatment means that the “source” of the radiation is placed on the outside of the patient given the treatment. Today, a linear accelerator is used to give the patients the intended treatment dose. This type of machine does not have a radioactive source, but instead accelerates particles (electrons) in a tube. The electrons can then be used to make high energy photon radiation (x-rays >1 megavolt, MV) used in treatment of cancer. Being steered by a computer the linear accelerator conducts high precision to both the intended target/volume and dosage placed in the patient. Energies from 6 to 15 MV are typically used in this kind of treatment, because of the therapeutic range of the radiation wanted when treating cervical cancer. The higher energy used the higher range of the radiation into tissue [16, 19, 20].

Planning this sort of treatment takes a lot of effort from oncologists, radiation therapists and medical physicists, and is done with precision with help from CT scanners, MRI scanners, and computer and picture programs especially designed for radiation treatment. The main concern when planning radiation treatment is to have a high as possible therapeutic ratio. This means that calculations are made regarding damage to healthy tissues, and reducing the dose to normal tissue as much as possible in contrast to the cancerous tissue. The goal is to lower the risk of damage to normal tissue at the same time as the chances of curing the cancer are increased [19, 20].

Treatment with radiation therapy of women with cervical cancer is mostly done with a curative purpose, and often given in combination with chemotherapy and/or surgery. Women that are treated with a curative purpose are treated from a treatment plan, made from a CT and/or MRI scan. In this way it is possible to tailor the treatment-volume that covers the tumor and any lymph nodes and parametrial tissue that needs to be included. By individually adapting the treatment-volume in each patient, the risk of long-term adverse effects after radiation therapy is decreased. The risk of developing adverse affects is also decreased by fractionating the external therapy, by dividing the dose in smaller doses over time, instead of giving few large doses. The typical treatment-regime for women with cervical cancer is a combination of external radiation therapy and internal (brachy) therapy [16, 17].

At Oslo University Hospital it is women with cervical cancer stages II-IVa that make out most of the women treated with radiotherapy. Radiotherapy treatment is also used in women with stage I that after surgeries are found to have removed too little tissue, metastasized lymph nodes or if there is a general concern for possible spread of the cancer. The external treatment is given as a so-called “box technique”, as shown in Figure 4 below, where four radiation fields are centered against the pelvis of the patient. A linear accelerator can move along the axis of a circle, 360 degrees, and when treated with a box technique, the machine delivers radiation at 0, 90, 270 and 180 degrees along this axis. The patient typically receives a dose of 50 gray (Gy), fractionated over 25 days in 2Gy fractions. The tumor-area gets a higher fraction-dose and the total dose is also higher than the nearby lymph nodes. In some cases it is desirable to give an extra dose to the lymph nodes or to parametrial tissue where the tumor size is large. Where it is detected that the cancer has spread to lymph nodes in the pelvic area, extended radiation-fields that covers possible ways for the cancer to spread via the lymphatic system, are given. This kind of treatment makes the radiation fields look like a

chimney, and is also called a “chimney” field. This treatment can either be given post-surgery or also as the primary treatment for the disease [16, 17, 21].



Label	#	Unit	Energy	FX (cm)	X1 (cm)	X2 (cm)	FY (cm)	Y1 (cm)	Y2 (cm)	X (cm)	Y (cm)	Z (cm)	Y Offset (cm)	Depth (cm)	SSD (cm)	Gantry (deg)	Arc Dir	Collimator (deg)	Couch (deg)	Wed
1	1	SB15	15.00 MV	<19.94>	<-9.68>	<10.26>	13.50	-6.00	7.50	1.00	5.00	0.00	0.00	12.70	87.30	0.00	N/A	0.00	0.00	
2	2	SB15	15.00 MV	<12.28>	<-5.60>	< 6.68>	2.85	-6.00	-3.15	1.00	5.00	0.00	0.00	12.70	87.30	0.00	N/A	0.00	0.00	
3	3	SB15	15.00 MV	<17.60>	<-7.42>	<10.18>	13.90	-6.20	7.70	1.00	5.00	0.00	0.00	21.25	78.75	90.00	N/A	0.00	0.00	
4	4	SB15	15.00 MV	<18.70>	<-9.58>	< 9.12>	13.90	-6.20	7.70	1.00	5.00	0.00	0.00	14.15	85.85	180.00	N/A	0.00	0.00	
5	5	SB15	15.00 MV	<17.85>	<-9.23>	< 8.62>	2.88	4.82	7.70	1.00	5.00	0.00	0.00	14.15	85.85	180.00	N/A	0.00	0.00	
6	6	SB15	15.00 MV	<17.15>	<-10.53>	< 6.62>	13.80	-6.10	7.70	1.00	5.00	0.00	0.00	20.87	79.13	270.00	N/A	0.00	0.00	

Figure 4: A typical “box-field” being planned from a CT-scan in a computer-program designed for radiotherapy [22].

3.2 Internal radiation (Brachy therapy)

Internal therapy or brachy therapy is a form of radiation treatment where a radioactive source is placed in the patient. Brachy comes from the Greek language and means “close”. This mirrors back to the facts that in every form of brachy-therapy a radioactive source with short therapeutic range is placed in close distance to the tissue of interest. Related to cervical cancer, intra or endocavitary treatment is the form of brachy therapy that is most often used. This treatment suggests that the radioactive source is placed in natural cavities in the body, like the vagina or the cervical channel. Another form of brachy therapy sometimes used in cervical cancer patients is interstitial therapy where the radioactive isotope is placed into the

cancerous tissue. This procedure is done via hollow needles (so the radioactive isotope can be introduced) placed into the patient by the oncologist [19].

Today, the radioactive source (isotope) mostly used in cervical cancer patients is Iridium (192Ir). This isotope has a short distance reach of transmitting its energy and the result is that most of the surrounding normal tissue gets much less dose than the cancerous tissue of interest. The Iridium is mostly inserted into the women via an applicator (or needles), that is led into to cervical canal, which again is connected to the apparatus that holds the isotope. Patients typically receive 5 treatments, fractionated to once a week, after approximately 15 external fractions. This type of treatment is given while the patient is sedated or is under anesthesia. The planning of the dose that is to be received is done by taking CT and/or MRI pictures after the applicator is put into the patient. Later the radiation treatment is given while the patient is lying in a shielded room with video surveillance. The isotope stays inside the patient between five and ten minutes [16, 19].

Brachy therapy can be used alone, but it is mostly used in combination with external therapy to increase the radiation dose to an area of interest. With external therapy, there are restrictions on how much dose the normal tissue can survive and it is sometimes difficult to get an optimal dose to the treatment volume. Brachy therapy can here be used to give an extra dosage to tissues it would be hard to reach due to dose-tolerance for normal tissue [19].

3.3 Effects of treatments - fractionation

As mentioned above, radiotherapy as a science is closely linked with both physics and biology. Effects of radiation are divided into the physical, the chemical and the biological phase, and can be seen from days to years after ended treatment. These effects are the result of either direct damage to the DNA-molecule itself, or radiation causing chemical and physical changes on a molecular level which again leads to damage to the DNA-molecules. A variation of direct radiation-induced damages can happen to the double helix that makes up the DNA-molecule [23, 24].

- Single chain breakage, where only one thread in the double helix are affected
- Double chain breakage, where both chains are affected
- "Cross linking"
- Change or loss of a base
- Change or total damage to sugar-molecules [23, 24].

The physical effect happens when high energy radiation changes the fundamental structure of atoms and molecules. Changes in structure lead to these molecules and groups of atoms having new chemical abilities. These powerful, but highly unstable groups of atoms become what are known as free radicals. The biological effects are a result of the physical and chemical effect-phases. This is the phase where the new chemical abilities in tissue lead to cellular death, mutations and damage to genetic material [19].

3.3.1 Cell-cycle, radio-sensitivity and radiation damage

Cells radio-sensitivity is closely linked to different sequences occurring in the time between one mitosis and the next (see Figure 5). In mitosis (the M-phase), the cell divides, chromosomes turns into daughter-cells and a new cell starts its life. It is in the M-phase cells are most radio-sensitive. Cells radio-sensitivity is dependent on maturity, therefore stem-cells and younger cells are more radio-sensitive than mature cells [18, 19, 23].

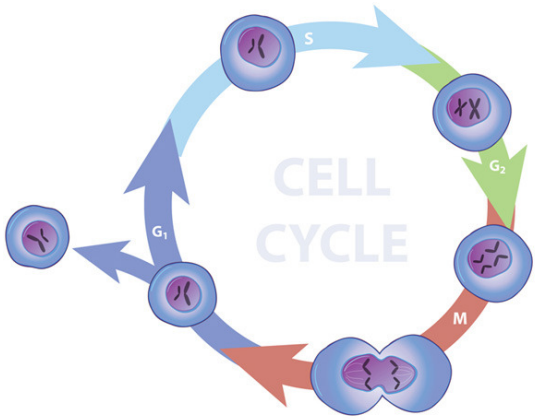


Figure 5: The eukaryotic cell-cycle [25].

The G1 and the G2 phases are so called “resting phases”. G1, where the cell prepares for division comes directly after the M-phase. G2 comes after the S-phase, and here the cell prepares for dividing chromosomes. The DNA-synthesis occurs in the S-phase where the amount of DNA is doubled. Younger tissues and organs and tissues with high metabolic activity are more radio-sensitive than other tissues. Frequent proliferation in cells, and high growth rate for tissues which is typical for cancer, result in high radio-sensitivity and greater cellular damage. The time period in which the biological effect occurs are also linked to how fast the cells proliferate. Normal cells have a better ability to repair any damage and mutation caused by radiation than cancerous cells have [18, 19, 23].

Cells will normally try to start repair themselves as soon as possible and to arrest the cell-cycle when exposed to radiation damage, this process gets activated within the cell the second a radiation-dose is absorbed by the tissue. This stopping of the cell-cycle gives the cell some time to get an overview of the DNA-damage induced, and possibly avoid mitosis so that any damage occurred may not be passed on to daughter-cells. An example of repair is when in single thread breakage, the cell is able to use the complementary chain as a template to build up the damage one. Needless to say, it is difficult for a cell to repair itself in case of a double-chain break [2, 23, 24].

Radiation-induced damage can be divided into several layers. Lethal damage leads to instant cell-death after being radiated since the damage is too great to repair. This happens either

when the cell can no longer divide itself or damage is detected and considered lethal so that the cell commits suicide by apoptosis. Sub-lethal damage is closely linked to dose and the time in between the radiation treatment. Cells are able to repair themselves at first, but damage increases with dose and may be lethal to the cell in time [18, 24].

Potential lethal damage is a condition where the cell might either die from the damage induced, but also potentially repair damage and live, or thirdly live on with the radiation damage induced. Cell-repair after this kind of damage is often regulated to population of cells that are not actively proliferating. It is if the cell will start its cycle and try to divide itself while still repairing that problem or potential death may occur. A potential lethal damage is correlated with dose, the higher dose the greater chance of repair, while how a population of cells repair themselves, is again dependent on the environment around such as temperature [18].

3.3.2 Fractionated treatment

Fractionated treatment is conducted because of the knowledge of radio-sensitivity throughout the cell-cycle. Cells that are situated in the most sensitive part of the cycle will naturally die first and the thought is that by making sure there are some time until the next treatment, another group of cells will be in the same part of the cell-cycle. Radiation therapy given with a curative purpose is always fractionated over days [19].

Another idea behind fractionated radiotherapy treatment is oxygen. We know today that the presence of oxygen makes cells more radio-sensitive. The problem occurring when treating cancer-patients is that all parts of a tumor rarely have the same access to oxygen, and cells with access to little or no oxygen, may be more resistant to radiation. Treating a tumor with radiation will lead to the oxygenated cells to get lethal damages, which again leading to the non-oxygenated population of cells increasing. At the same time it is known that all the interactions on the cellular level actually make use of oxygen, and it would be wise to let it go some time until the next treatment so that the build-up of oxygen has increased once again, and that the parts of the tumor that where non-oxygenated is now richer in oxygen and is more radio-sensitive [19]. A negative aspect with the process of re-oxygenation is the possibility that former hypoxic cancer cells may regain the ability to proliferate [2].

Lastly, the thought behind fractionating the treatment is to make sure that the normal tissue cells are able to repair any damage between each treatment, so that potential side-effects are as small ass possible. Normal tissue has better ability to repair itself than cancerous growths have. This is generally because cancerous tissues are often are made up of hypoxic cells. A time limit of four to ten hours between each fraction (depending on the type of tissue) is set to make sure normal cells can repair themselves [19, 23, 24].

3.3.3 Radiation-effects over time

Tissues where cell proliferation are high (time-period from one mitosis to another is short), will typically show effects from radiation first (as damage induced by radiation therapy mostly shows itself as the cells try to divide). These types of tissues are for example present in the bowel, the central nervous system or in mucosal membranes. Different tissues consist of different cells that have different cycles from hours to days to years and potential lethal damage may not show until the cell try to divide itself [19].

Side-effects from radiation are often divided into acute and chronic (late) effects. In normal tissue, it is cells with high proliferation that resembles cancerous tissue that often make out the acute side-effects from radiation therapy. Damage to these kinds of normal tissues can be difficult to avoid using any type of fractionated treatment, as they have a fast cell-cycle and often find it hard to repair any damage caused directly or indirectly from the radiation before the nest treatment. When planning radiation therapy this is the Occam's razor of this kind of treatment. One needs to be treated with such a dose and fractionation-pattern so that it kills of the tumor-cells, and at the same time try to avoid damage to the surrounding normal tissues. Radiation-therapy would not exist as a form of treatment for any kind of disease if damage to normal tissues where zero tolerance. Radiotherapy today is based on what is clinically proved to be the tolerated dose to surrounding tissue and how high of risk is acceptable, also to the patients [19]. Acute effects may be a difficult experience for patients during treatment, but will not cause any problems over time [20].

Normal tissues in the human body also consist of cells that proliferate slowly, do not divide themselves at all unless they have to or do not proliferate at all. These are the types of tissues that might show what is called late-effects from radiation. The effects can show up months

after treatment and might even get worse as time gets by. Damage has been present in these cells the whole time, but has been hidden since no form of proliferation has been ongoing. As soon as one cell in this normal tissue starts to divide and then dies its neighbor cell will experience the same. It is very hard to stop or even slow down this process, and it will continue until a scar is built, and the damage becomes a chronic condition [20].

Even though some tissues in the body consist of non-proliferating cells and may be low in radio-sensitivity, it does not mean that a tolerance dose does not exist. Muscle-tissue is for example mostly made up of these kinds of cells, but if the tolerance for radiation dose is bypassed it will cause a chronic late-effect [20].

4 Late Effects

Combinations of surgery, chemotherapy, radiotherapy have the recent years increased the survival-rate for women with cervical cancer [26, 27]. More long-time survivors also means there are today several challenges for health-personnel to rehabilitate these women back to every-day life. How severe late-effects may become varies between treatment modalities and also the individual patient. When late effects do become chronic, the main concern is to treat the symptoms, as the effects of treatment here have become a chronic and life-long condition [20].

Basically all treatments offered to women with diagnosed cervical cancer can have adverse effects on their sexual function [11, 15, 28]. Surgery, the number one treatment modality, will in most cases lead to removal of the cervix along with upper part of the vagina, and some women are prone to experience a shortened vagina by for example pain with intercourse [10, 11]. A radical hysterectomy will of course lead to infertility [28]. It is today not a normal procedure to remove ovaries in women with cervical cancer, but many women will undergo high-dosage of radiotherapy and sometimes also (in combination with) chemotherapy. Adverse effects from radiation may be acute, but effects from high-dose treatment may also occur 5 years or more after treatment. Surgery, radiation and chemo-therapy may all damage the ovaries hormone-producing ability, which in case leads to hormone-levels decreasing, the woman experiencing early menopause with sudden symptoms like hot flushes and dry mucous membranes [10, 11]. Menopause as a late effect also means the woman will be infertile [28].

Vaginal dryness and lack of hormones could lead to bleedings and pain, not least with intercourse, and an increased risk of infection [10]. High doses of radiation against the vagina could lead to vaginal atrophies, vaginal stenosis and that the elastic ability of the vagina is no longer working properly [11, 28, 29]. Generally, high radiation doses against the pelvic area may lead to scarring of tissue [30]. Radiation against the mucosal membranes of the bladder may lead to problems with cystitis, increased risk of infections in general and in some cases chronic incontinence. Radiation induced effects to the bowel in the pelvic area occur, and may

lead to chronic diarrhea and malabsorption. Many patients experience both small and large bowel problems as a result of high dosage of radiation [28, 31-33].

Some women may experience after surgery and radiation therapy that fistula occurs from the bladder, the bowel and the vagina to nearby organs in the pelvis. Many women are troubled with smell and seeping from the bladder and/or the bowel as a result of this. In addition to increasing the risk of infection, it is problematic both physiological and psycho-social to maintain a healthy sexual life [15, 28].

5 Cancer and Sexuality

"Sexuality is a central aspect of being human throughout life and encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction. Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviours, practices, roles and relationships. While sexuality can include all of these dimensions, not all of them are always experienced or expressed. Sexuality is influenced by the interaction of biological, psychological, social, economic, political, cultural, ethical, legal, historical, religious and spiritual factors."[34]

Sexuality as an aspect in our life is a powerful force of nature. Despite if it is being lived out or not it is an important piece of the human identity, and all health-workers should understand the fact the every being is a sexual being despite age, gender and life-situation. Sexuality may increase the feeling of cohesion and coexistence with other people in addition to strengthen sexual identity, safety and quality of life [35].

Sexual dysfunction can be defined as

"a malfunction of organic, psychological or mixed character that stands in the way of individuals or couples sexual motives in a uncomfortable and/or painful manner"[36]p158

Almås and Benestad says that by integrating a sexual wakefulness into our everyday life, it is possible to better a patients sexual function if it should be reduced of influenced by disease or treatment [36].

In a bio-medical perspective cancer has always been seen as a very "bodily" or physical disease. The disease (and the treatment) destroys bodily functions as it progresses. Cancer may impact the feeling of identity in its host as a result of this, and it is therefore not surprising that patients sexual life also are implicated [29]. Sexuality is an aspect that is largely connected to self-worth, quality of life and last but not least identity. It can touch the private sphere through the fact that sexuality is something intimate and woundable, and cancer resulting in a reduced sexual function may affect the human being [37]. Although cancer may change the bodily dimension with physical changes as it progresses, sexuality and

how patients cope with changes (that may be life long) regarding to it, is also highly subjective [29].

"Sexual health is a state of physical, emotional, mental and social well-being in relation the sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. For sexual health to attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled."[34]

The majority of people diagnosed with cancer will experience a negative impact on their sexual health. Cancer is sometimes divided into the three stages based on the time-lapse of the disease. The examination-period leading up to a certain diagnosis are often related to uncertainty and anxiety. The treatment period leads to a number of side-effects such as insomnia, pain, nausea and dysfunctions. During this time, sexuality is often an aspect that is not important, since the aspect of surviving is the priority for most patients. It is often in the rehabilitation-period where the patient (and any partner) is supposed to learn how to get back to "normality" with new roles ("cancer-survivor") and a new life-situation that the meaning of sexual health and any sexual dysfunctions may appear [38].

How negative sexual functioning and health affects patients are sometimes related to age. The majority of all cancer-patients are over 65 years old. As patients get older, the importance of genital sexuality is generally reduced, but it is a known fact that there are huge individual differences. Older patients as well as younger patients may feel that their quality of life have been reduced as a result of a reduced sexual functioning [29]. Cervical cancer has a lower mean-age than many other types of cancer [1]. Sexual functioning is often a really important aspect for younger patients, related both to infertility, how they view their own body physical and mentally and again their identity [29].

Aspects of side-effects related to sexual health after cancer are often divided into three parts; physiological, psychological and psycho-social. Physiological side-effects are characterized as physical symptoms such as vaginal dryness, infertility, hormonal changes, narrow or shortness of the vagina, pain, nausea, fatigue, incontinence and artificial menopause. Physical symptoms of side-effects are related both to the disease itself and the treatment for it [29, 37,

39]. Kristensen claims that about 50 % of patients treated for cervical cancer will experience ailments related to sexual functioning [28].

Psychological side-effects may be every aspect from a change of sexual identity, body image disorder, and anxiety and raised wound ability to feelings of shame, unworthiness and emptiness. Psychological side-effects of cancer and treatment has been said to be the main cause of dysfunctions [40]. Particularly cancer located in the pelvic region in women (and men) has been known to cause a feeling of loss of femininity (or in men's case, masculinity). Loss of feminity is closely linked with women's feeling of self, sexual self-worth and attractiveness. Cancer may cause a rupture in any of these aspects and induce sexual dysfunctions [29, 41].

Psychosocial side-effects can also be induced by cancer and treatment. Side-effects such as a change of roles in relationships, reflexive sexuality, isolation, behavioral changes (includes sexual), dependency and avoidance of intimacy are not uncommon. There is also the possibility that physical pain, unpredictable life-situation and loss of identity may lead to anxiety and depressions [29, 39].

The three parts of side-effects mentioned here may be closely linked. It is possible that physical side-effects can cause psychological reactions, which again, turn into psychosocial changes. Borg claims that loss of femininity may cause a variation of grief depending on how important sexual functioning and health was for the patient from the beginning. It might turn into a self-fulfilling prophecy, giving feelings of non-attractiveness and unworthiness time to grow. Grieving ones sexual functioning may lead to guilt, shame and isolation [36, 42].

5.1 Silence in the medical field – Myths and stigmas on cervical cancer

In contrast to what popular culture and society today in general may reflect sexuality, sexual health and particularly sexual dysfunctions are still today "silent" and taboo themes, also amongst health-workers. In many cases, information given to patients today about side-effects from disease and treatment are unfulfilling when it comes to information about sexual health [29, 36]. Juraskova et al. found that the majority of women participating in their qualitative

study felt that the medical personnel they met over-estimated the women's knowledge about their own body and bodily functions when it came to information given about side-effects of treatment. This would lead to misunderstandings when experiencing the different modalities of treatment or a combination of them [43]. It is also a known fact that many health-workers are more attentive to male sexuality than to the female. This may be a large contributor to upholding or creating myths about cancer and sexuality, such as cancer cells can be transmitted from person to person or that sexual activity in any kind can cause a more aggressive cancer [29, 36]. Several women in the study conducted by Burns et al, felt anxious about resuming to the sex-life they had before treatment, partly because they thought this might invoke the cancer:

When I went to the hospital you know, they ask you all these different things and he said are you having sex. Well I was always afraid because it might start bleeding again. Will it hurt me kind of thing [44]p 368.

In Bilodeau and Bouchards phenomenological study on women with cervical cancer, women address the awkwardness associated with talking about cervical cancer that "one gets through sex":

I got cancer (…) a virus which one gets sexually. It is as I begrudge myself for letting myself being swept up by this liberating sexuality that I had, for having so much pleasure that I ended up having cancer (…). (Francine)[45]p235.

So the doctor tells you: you must have caught a venereal disease to get this cancer. The only man I ever slept with is my husband. So, its not me who went out there to get it (HPV). So I resented him for that. (…) It took six months for my grudge to disappear. (Jeanne)[45]p235.

A number of studies both amongst health-workers [46], and patients [44, 47], reflects the need for better communication on this topic. It has been discussed whether the aspect of communication about sexual health is a patient or a personnel problem, but it is a widely regarded view that many health-workers feel that sexuality is a topic that crosses their

personal boundaries or competence and causes uneasiness or they simply do not regard sexual health and functioning as of any importance for the cancer patients' quality of life [29].

The Danish study of Gyrtrup et al. amongst nurses, showed although most of the nurses personally thought that sexuality was an important issue, very few chose to inform, guide or speak to their patients about it. In Norway, Anna Aaneruds study from 1993, showed that only approximately 25% of women with cancer where informed about disease and treatment and how it would affect their sexual health [46, 48].

Graugaard et al., claims that health-workers should take the first initiative and introduce topics such as sexual functioning and health for the patients. It is further claimed that only by doing this, will we be able to remove long existing myths saying that all ill patients are asexual [38]. It has been claimed that myths like the one above and prejudice thinking are the real reasons for silence amongst health-workers. Hospital personnel thinking that survival is the only important aspect in patients' life and therefore not bringing up the topic may result in the fact that patients assume sexuality is in fact a non-topic and then go on living with her problems. Fact is, most patients are influenced by this norm if it exists in the ward thus are personnel pushing their own personal barriers over on the patient [49]. Skårderud says that shame is closely linked with silence. Shame is something that is seen as private and has to do with self-unworthiness. A person that feels shame is expecting to be met with other people's contempt, not with their care and compassion [50]. By introducing sexuality and sexual health to the patient early on in the disease, a door has been opened up for communication, guidance and support if and when the patient may have the need for it [49]. Lastly it is also important to remember as a health-worker, that even it is implied that sexuality and sexual health and function are aspects to inform the patient on, not all patients have the need or feel comfortable with conversations about these topics. Their decision should be highly respected [35].

5.2 Sexual Rehabilitation

Even though the majority of medicine today (and this master-thesis) is bound to the bio-medicinal model, it is important to remember that even though the patient may present with symptoms of the somatic kind, the key to sexual rehabilitation is a holistic way of treatment. The bio-psycho-social model was developed by psychiatrist George Engel in the 1970s. His

thoughts where that human behavior could not be separated into one single element, and that understanding lay in the fact that behavior is based on a dynamical coexistence within overlapping dimensions; in sexuality biological, psychological and social. Excluding one or the other dimension when trying to help patients with sexual rehabilitation, may lead to loss of information and a result of inferior quality [38].

There are a number of sexual aids that might be helpful to women with cervical cancer today. Introducing sexual aids as an idea, and making things better, require a good deal of adequate information about how the work and sexuality in general. It is unfortunately known that the ability for different wards in hospitals regarding information and counseling are varying. In Norway, women undergoing pelvic radiation are to be given “toiletry” that consists of a vaginal dilatator (two different sizes), lubricants and condoms. The use of the vaginal dilatator is to avoid vaginal stenosis and help keep the vaginal walls open and elastic by treatment of dilatation, during and after the radiotherapy treatment. Needless to say, the idea of making this work requires more then just delivering the “toiletry”. Information needs to be given about the why, the how and the when; also to any partner the patient might have [29, 51]. Studies have shown that women who do not make use of the vaginal dilatator have greater risks of developing sexual dysfunctions [52]. Drugs such as lubricants and estrogen crèmes or tablets might be helpful with vaginal dryness. Hormonal damage might be permanent after radiation treatment, and many women might benefit from supplementary hormonal drugs, to help with both desire-issues and vaginal dryness [38, 51].

Shortening of the vagina after surgery, with or without radiation treatment, can cause pains with intercourse, and patients need information regarding this. Survivors and their possible partners should be informed that a longer foreplay may be needed and that a sexual position that gives a shallower penetration is a better option to avoid any pain [28].

5.2.1 The PLISSIT-model, Sexual Counseling

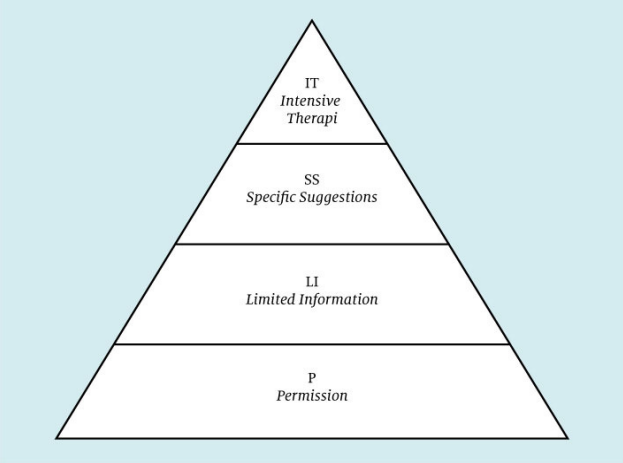


Figure 6: The PLISSIT-model of Sexual Counseling [53].

The PLISSIT-model (Figure 6), was developed by psychologist Jack Annon in 1976, and is often used in treatment of sexual problems, both educational, counseling and treatment-vice. Originally funnel-shaped, this model is often depicted in literature as a triangle with four different levels. Each level describes different solutions of sexual problems. The model in its self can also be used as an evaluation of level of professionalism, knowledge, competence and the experience that is needed to provide a patient with the right kind of guidance for his or hers problem [36, 54].

The first level in the triangle is called “Permission”. Permission indicates that the patient is permitted to be a sexual being, in other words sexuality is here acknowledged as the normality. The majority of patients seeking help for either prevention of sexual dysfunction or sexual dysfunctions may benefit from simple suggestions regarding their situation, and belongs to this level. Graugaard et al 2006, claims that by giving patients permission to talk either verbally or non-verbally about their sexuality and sexual health is the majority of what sexual counseling is about seen from a PLISSIT-model point of view [38, 42, 54].

The second level “Limited Information” indicates literally that the patient is given a limited part of information about her situation and/or medical problem. Any myths, questions or misunderstandings about disease and sexuality are clarified. It is the patients or any partners’

response to the first level that indicates if the sexual counseling should go up to the next levels [54].

On the third level “Specific Suggestions”, the patient is often given specific solutions or suggestions regarding her sexual problems and sexology treatment may be started. An example of specific suggestions may involve the use of sexual aids and how they are used. It is also on this level where some professions may refer the patients to further expertise in the field. On this level, it should be noted that, as a health-worker, one now balances the edge between guidance and therapy, and it is important to know the professions limitations. The top level “Intensive Therapy” requires specialist competence, and may involve general medicine, surgery and/or psycho-therapy [54].

Many cancer centers offer courses for women that focuses on the slogan “look good, feel better”, where women get advised about make-up, hair perfumes etc. Some cancer centers also offer courses related to cancer and sexuality, often in association with Vardesenteret [29, 55]. Vardesenteret was established by the national cancer association; Kreftforeningen and Oslo University Hospital and is now located in Oslo, Trondheim and Tromsø. The original purpose of the center was:

”To give patients with cancer and their relatives a care service meeting today’s and the futures need for a holistic cancer care.”[56].

In Norway today, sexology counseling and guidance after cancer, is offered to men and women with any partners they might have at Vardesenteret at Radiumhospitalet. Counseling is conducted by a sexologist educated by guidelines of the Nordic Association for Clinical Sexology (NACS) [55].

6 Systematic review and meta-analysis as methods to define effect

The idea of combining different results from different studies both qualitatively and quantitatively is older than the terms systematic review or meta-analysis in them selves. Statistic Karl Pearson analyzed small studies about the use of vaccines for typhoid-fever already in the early 1900s. Gene Glass collected studies on the effects of psychotherapy in the 70s and managed to get his results published and respected in larger parts of his field. Since then work has progressed to make the method more reliable by developing solutions on how to meet methodological challenges like validity and heterogeneity when combining different studies [57].

A systematic review can be seen as a systematic approach to literature. It summarizes and evaluates different studies on the same matter in a specific given way [58]. Another definition is that a systematic review is

"…a review that has been prepared using a systematic approach to minimizing biases and random errors which is documented in a materials and methods section"[59] page 5.

The Norwegian Knowledge Centre for Health Services has developed three criteria to make a review systematic, based on the thought that it should always be possible to criticize and revise samples, results and conclusions made in the review [58].

- The review needs to state a defined electronic search strategy.
- The review needs to define criteria set for inclusion.
- A methodological quality assessment must be made of the studies and/or reviews included [58].

A systematic review does not always include a meta-analysis. This is due to the fact that it is not always appropriate and/or desirable to combine data found in articles. Studies included might be too different, and instead of being included in a meta-analysis, results and effect-size

should be described in the narrative way. Combining results that clearly should not be combined could be deceptive and in health-studies clinically misleading [59].

A meta-analysis is a statistical approach to summarize results from the independent studies in a systematic review, and it is most common that results from the analysis in presented in one single estimate such as odds ratio or risk ratio of treatment effect [59]. A meta-analysis is effective and there is no limit on how many studies can be included. Because of study-variation, there is bound to be some differences or heterogeneity between them. This could be due to differences in population, outcomes and/or measures also called clinical heterogeneity, or methodological differences such as differences in designs or the risk of if the bias between studies included are due to random effects or not [58].

A meta-analysis can account for different sizes in independent effects and populations, and it is possible to determine and study variations and heterogeneity in studies as well as clarify any inconsistent results found. The quality of a meta-analysis is dependent on the methodological quality of the independent studies included in it [57].

Producing a systematic review can also give an indication as to if more specific and sufficiently sized trials are needed in certain disciplines. More evidence is always needed to provide patients with new, better and individualized treatment options [59].

It is common in medical treatment and/or effect studies to use dichotomous variables. An example of this could be in a randomized control therapy study where one part of the population received treatment and the other received a placebo-drug. Another example, as used in this master thesis, is one part of a specific population receiving a certain treatment and another healthy part (control group) of the same population did not. There are several estimates for measuring effect. Results from the meta-analysis could exemplified be given as odds ratio or risk ratio (in this thesis), alternatively percentage or proportions [57].

Risk-ratio or relative risk can be seen as:

The estimated proportion of the original risk for an adverse outcome, that persists when people are exposed to the intervention [60] p 573.

6.1 Systematic reviews of observational studies

Combining individual observational studies like cohorts and cross-sectional studies like in this thesis are always linked with a greater chance of producing a well defined, but deceptive overall estimate of a treatment effect. Even though randomized controlled trials (RCTs) are seen as the gold-standard in research designs, there is however a need for observational studies, since RCTs do not have the capability to study for example hypothesis of the etiological kind and medical effectiveness over time [61]. A cross-sectional study is a study conducted on a section of a population. This type of study is unable to say anything about the cause, but rather measures occurrence and distribution of a phenomena at a given time [60]. A cohort study on the other hand, has the ability to follow up on changes over time, measure incidence of disease and look at more than just the outcome. It is possible in this type of study-design to observe the context of different phenomena [60].

6.2 Estimate effect – Fixed or Random Model

The use of a fixed model assumes that all studies included are of equal interest and that any variation between them is ascribed as random chance. The goal of this model is to estimate a general treatment effect. A weakness in the fixed effect model is that included studies with a large patient population get weighted higher than other studies. When summarized with other studies in a fixed effect model, the study with a large population will be weighted at a rather larger scale than the others and thereby the results from this study will be dominating [60].

By using the random effects model when summarizing treatment-effect with risk ratio, one makes an educated guess that the treatment-effect between studies included varies, but follows the same distribution. A limitation using this model is that quality of studies may be correlated to size, and smaller studies with lower quality get their results weighted to high [60].

6.3 Other methodological challenges

When doing a systematic review, and including meta-analysis, there is also the possibility of publication-bias. There is also a greater chance for publication bias in small studies than there is in larger ones. Studies published in other languages than English also gets less attention, can be harder to find when conducting a literature search and may not even be indexed in data-bases like PubMed. In addition to this, one should also know about both scientist and journal censorship, when it has been known to happen that non-significant results do not publish as a result of scientists censoring themselves [62].

Another possible bias is happening when studies that are highly significant either in the negative or positive way gets published in large respected journals, whereas smaller studies with swinging results may not make the large databases and journals. In this way, it is possible for systematic reviews to exaggerate or undermine effects of treatment (Polit & Beck). Period effect can occur and lead to mistakes when studies that take place over a greater period of time are included in a meta-analysis. Changes in treatment and therapies can make it hard to interpret the ending results. A possible solution is to only include studies from set years, so it is possible to see treatment-effects over time [62].

7 Results

In this section of results, a larger narrative description of findings will be presented of all nine observational studies included, as an addition to the results and meta-analysis presented in the article.

In the study conducted by Bergmark et al., no significant differences where found in sexual interest between controls and/or the different treatment groups. In addition to this no significant differences where found regarding pleasure, frequency of intercourse, and/or orgasm. The patient group as a whole, (S, RT or both), reported significantly more problems with vaginal dryness than the control-group. No significant differences where found regarding vaginal dryness between patients having surgery only and patients receiving only RT and/or in combination with surgery. Problems with shortening of the vagina were reported significantly more in the patient group as a whole than in the controls. It was found when comparing patients that received any combination of RT vs. surgery only that 19 % of the surgery patients had this problem, whereas approximately 30 % of the RTs encountered the same problem. The study found out that the majority of women with cancer experiencing decreased sexual function become stressed out over the negative aspect diagnosis and treatments have on their sexual life. Having a sexual life was of value to every age-group in this study and the importance for health personnel to be aware of this was highlighted by the authors. The study could not conclude that the choice of treatment-modality had any impact on the prevalence of specific vaginal changes [63].

Cull et al. conducted a retrospective cross-sectional study and when comparing their life before treatment, about half of the women included in the study felt like their sexual function had deteriorated. All phases of their sexual response-cycle where involved, including sexual interest, frequency of intercourse, arousal, lubrication, pain with intercourse (dyspareunia), and sexual enjoyment. All differences measured before and after in sexual functioning where highly significant ($P<0.005$). When looking for differences between treatment-groups (RT vs. S) an adjustment for age and pre-morbid function where done, and conclusion was that RT patients significantly more often reported dyspareunia ($P<0.01$) and loss of sexual pleasure ($P<0.01$). Many women in this study had worries of pain with intercourse, intercourse leading

to the disease returning, lack of attractiveness, lack of sexual attractiveness. About 1/3 blamed their partner for their cancer-disease, whereas more than 1/3 felt that the having cancer was their own fault [64].

Patients included in the study carried out by Donovan et al. reported a significantly worse sexual health than the women in the control group. Patients experienced a significantly higher loss of sexual interest, more sexual dysfunction and less sexual satisfaction when compared to the healthy control group. No significant differences where found between patients with cervical cancer and healthy controls regarding sexual activity during the last year. Patients treated with RT reported significantly more sexual dysfunction than women treated with surgery only. The most prevalent predictors for sexual health after treatment were; time since diagnosis, RT, partner relations, perceived physical appearance and vaginal changes [65].

Frumovitz et al. found in their study that patients treated with RT had a significantly worse overall sexual function after treatment than both surgery patients and women in the healthy control-group. Irradiated women had problems concerning becoming sexually aroused, vaginal dryness, reaching orgasm and also achieving sexual satisfaction. Women treated with RT also reported significantly more dyspareunia than women treated with surgery and healthy controls. No significant differences where found between the three groups regarding sexual lust. Patients who received RT had significantly higher score on overall menopausal symptoms such as hot flushes, vaginal dryness and urination problems, compared to both surgery patients and healthy controls. No significant differences where found between the 3 groups in relations to dating or committed relationships [30].

Greimel et al. found in their study that patients treated with both surgery and RT, scored significantly lower on the sexual activity rate than the two other treatment groups ($p=0.006$). No statistically differences where found among the groups concerning sexual pleasure and sexual discomfort. Irradiated women also had significantly more problems with symptoms as frequent urination, leaking of urin and the feeling of having a tight/narrow vagina [66].

Jensen et al. followed a group of women treated with RT for CC up to 24 months after their treatment ended. They found than after twelve months, sexual interest was reduced for patients with 64/74 (87 %) compared to 128/218 (59 %) for women that where in the healthy control group, but this measure was equal to healthy controls from 3-24 months after

treatment for most patients. Low or no sexual interest was reported by approximately 85 % of the patients during the time aspect in the study [67].

Lack of lubrication was for control 7/133 (5 %) vs. patients 10/25 (40 %) at 12 months. 35 % of the patients reported moderate to severe lack of lubrication during the study [67].

Further it was measured that over the first 12 months, dyspareunia in controls (measured quite a bit - very much) was 5/144 (4 %) vs. the patient group 4/24 (17 %). Mild to severe dyspareunia on the other hand, was reported by approximately 55 % of the patients over the whole 24 months after treatment [67].

Size of vagina bothersome during intercourse, where for controls 12/138 (9 %) vs. patients reported 7/24 (29 %) at the 12 months measure time. A reduced vaginal dimension was reported by approximately 50 % of the patients during the 24 months after treatment [67].

Klee et al. found that the outcome-measures vaginal discharge and irritation around the vagina where mostly acute symptoms with a high early score that returned to the same level as the healthy controls as time passed by after treatment (24 months). The patients experienced frequent voiding as both an acute, (just after treatment), and a chronic side-effect two years after treatment. Those patients who experienced the symptom as an acute effect had an all-time high at 3 months after treatment. Although diarrhea was a symptom that a large part of the patients experienced, there was no indication for having the symptom becoming chronic later on. The number of patients that initially had high levels of diarrhea, declined during the first 3 months. The study showed that a significant part of the patients will develop chronic diarrhea [68].

In Park et al. it was found that the different treatment groups reported significantly worse body image, lower sexual and vaginal function (especially for RTs), more sexual worry and more clinically severe experiences of symptoms than did the healthy control group. Lymphedema was significantly worse in all treatment groups, and it seemed like patients that received surgery and RT combined where worst off. Also peripheral neuropathy and symptoms related to menopause where significantly worse for the cancer survivors and especially patients that where treated with RT [69].

Anxiety related to sexual performance where significantly higher in the survivors, no matter what kind of treatment given, when compared to controls. When looking at treatment groups

given RT compared to surgery only, patients treated with combined RT and surgery where significantly more likely to report anxiety related to performance than the other groups [69].

Pain during sex was significantly higher in patients treated with RT compared to controls. When compared to surgery only, this was also the case in patients treated with combined RT and surgery. Women treated with combined RT and surgery had a significantly worse score in sexual interest, vaginal dryness and pleasure during sex than women only treated with surgery. No significantly differences where found between the treatment groups and the controls in sexual activity and sexual enjoyment. No significant differences where found between controls and/or treatment groups in not being able to achieve orgasm [69].

Pieterse et al. found that after 3 months, a significantly larger percentage of patients treated with RT, where less sexually active than patients only having surgery. During the first 24 months after treatment there was a significant large part of patients that reported dyspareunia, short/narrow vagina, vaginal dryness and general dissatisfaction with their sexual relationship, than before treatment. This was significant compared to healthy controls throughout the 24 months. No significant differences where found between treatment groups in the variables dyspareunia, sexual satisfaction and vaginal dryness [70].

8 Statistic significance versus clinical significance

In the discussion-part of the article, reasons where explained for the choices made in relations to methods and analysis in this master thesis. This chapter will elaborate a bit more on certain aspects regarding discussion on results from this study related to the relevance of systematic reviews.

Unfortunately it is not the case that statistic significance obviously can be translated into clinical significance. Just because a study finds a significant change does not mean that it is relevant when implemented into a clinic. Feyers and Machin wrote about studies on quality of life, but their thoughts on assessment, analysis and interpretation can easily be used on sexual health and functioning [71, 72] In this study a systematic approach was taken as to avoid biases as much as possible, but like studies on quality of life, sexual health and functioning are measured with subjective questionnaires.

A weakness, when trying to find any clinical significance in results from this study is that the different studies included uses different measures and scales to define what is reduced sexual functioning and what is not. An equal score on two different scales in two different studies may not signify the same level of sexual functioning, but then again, when conducting a meta-analysis, one would control for this. Assessment tools where used in this master thesis to evaluate methodology for each study included. A score for reliable outcomes measured was given if questionnaire used was validated.

A challenge linked to the use of subjective questionnaire as an instrument, is the phenomena "response-shift". Most individuals facing changes in their health-situation are affected by this phenomenon, and it is important as when interpreting results from a study to realize that concepts like health and function may be dynamic over time. Faced with a serious illness human beings have a tendency to change their inner principles, values and understanding of their own health and functions. Response-shift can be especially relevant in studies conducted over time. As patients conceptualization regarding their own health and function may change over time, so might answers to questions asked. Results can thereby be influenced by the fact

that answers over time may be difficult to compare. Changes in response are common in the cognitive (satisfaction, achievements, cognitive abilities) and subjective areas (pain, interpersonal relationships, fatigue), and may greatly influence adaption to living with a serious illness/disease [72].

Even though all of the studies included where given a fairly high score on methodology, measures for heterogeneity where expected to be, and sometimes measured a bit high. Studies included where all observational studies with differences in sample sizes, patient criteria (disease stage/age/treatment). A small or large sample-size could be of relevance when evaluation clinical relevance. Also a sampling of patients randomly or continuously as they are introduced to the health care system could affect in what grade it is possible to make a generalization in this patient-group as a whole. The choice of criteria for treatment and age could also be an important factor [72]. The majority of studies included into this study had made adjustment for age in their analysis.

When evaluating systematic reviews in a clinical setting whether it is dealing with the individual patient, the making of clinical guidelines or determining health-resources, it is always a challenge to evaluate if results deriving from a review, (a wide range of patients), are applicable. In addition to assess all outcomes, negative and positive, and possibly do a grading of the evidence, clinical judgement, can also ble useful when determining the risk factor in an individual patient and/or making guidelines. Results deriving from systematic reviews looking at adverse effects might be beneficial to patients. Health practice today is trying to implement patient autonomy and the patients rights laid down by the law to be informed and included in aspects and decisions regarding their own illness and health. Possible positive and negative effects from illness and treatment should be communicated in an informative way so that patients can make choices based on knowledge [73-75].

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Appendix II

Gynecologic Oncology - CHECK LIST FOR AUTHORS

Required Submission Criteria

Order of Submission

The order of your new submission should be as follows:

1) Cover Letter

2) Conflict of Interest Forms

3) Manuscript File (should include title page, abstract, full manuscript body text, conflict of interest statement, references, and table and figure legends)

4) All Regular Tables (in order of citation within the manuscript text)

5) All Regular Figures (in order of citation within the manuscript text)

6) All Supplementary Materials (including video submission)

7) Highlights

General

□ The limitation on the **number of authors** has been observed. If not, detailed information on each author's contribution to the manuscript is outlined in the cover letter. Original Research Reports have a limit of 10 authors, while Reviews have a limit of 5, Video Submission, and Letters to the Editor have a limit of 3. If you have more than the limited number of authors, you must provide justification in your cover letter. The justification should include a detailed list of each author's contribution to the article. If the handling editor feels that the number of authors is excessive, you may be asked to remove authors from the submission. Please note that if you add authors (beyond the limitation) at the revision stage, justification must be provided as well as a signed conflict of interest form for each new author. After your article is accepted, you may not add authors to the manuscript without prior approval from the editorial

office. To determine authorship of manuscripts submitted to *Gynecologic Oncology*, please use the following criteria provided by the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (available from Secretariat Office, American College of Physicians, Independence Mall West, Sixth Street at Race, Philadelphia, PA 19106-1572).

□ Suggest at least **two potential reviewers** who are experts in the field and provide reviewer's full name and current functioning email addresses for each.

□ Provide a **cover letter** that outlines the significance of the findings, the contribution of the individual authors, and any other information pertinent to the review and publication of the manuscript. If your paper has more than the allowed number of authors for the article type, your cover letter should also provide detailed information regarding each author's contribution to the article. All financial support should also be stated in the cover letter.

□ **Conflict of Interest Forms** for all authors are signed and included with the submission. Please note that manuscript will not be seen by editors or reviewers until all conflict of interest forms are included with the submission. Forms may be downloaded here: http://www.elsevier.com/framework_products/promis_misc/Gynecologic%20Oncology%20Conflict%20of%20Interest%20Policy%20Form.pdf

□ A **Conflict of Interest statement** is included in the main manuscript file and appears before the reference listing

□ **Pages are numbered** consecutively

□ **Lines are numbered** consecutively. All line numbers should be provided on the left margin of the page, and each and every line should be numbered. Please number all pages continuously and do not restart the line numbering on each page. You may add line numbers in Microsoft Word by clicking on "File", select "Page setup", select the "Layout" tab, click on the "Line Numbering" button, check the "Add Line Numbering" box, and select "Continuous"

□ **Lines are double-spaced**

□ **Word count / table & figure limitations** are observed both on the abstract and on the manuscript text.

MANUSCRIPT LENGTH AT A GLANCE

Article Type	**Abstract Length(words)**	**Manuscript Length (words)**	**Tables and/or Figures***	**Supplemental Material**
Original Research	250	3000	6	No Limit
Review	300	4500	6	No Limit
Editorial	N/A	1600	N/A	No Limit
Clinical Commentary	N/A	1600	N/A	No Limit
Letter to the Editor	N/A	1200 (8 refs max)	N/A	No Limit
Video Submission	250	4 refs	max 1 (Figure still)	No more than 100MB

*A combination of figures and/or tables is permissible.

□ The manuscript is **written in clear and proper English**.

□ Research Highlights should be between 2-3 bullet points and should be no more than 85 characters including spaces for each bullet point provided in a separate file.

□ All files are presented in the **proper order**. Files should be ordered according to the number which appears next to the file description on the “Attach Files” screen.

Title page

□ Every submission must include a title page as the **first page of the manuscript file** (please note: not the system generated built PDF, but rather the Microsoft Word document or RTF file that you upload to your submission). Please note that the corresponding author listed on your title page must match the corresponding author entered in our systems; should this information conflict, we reserve the right to contact either or both authors for correspondence.

□ Includes **full title** of manuscript.

□ Includes **all author names** in the style and order to be published.

□ All **current author affiliations** are provided.

□ The **corresponding author** is denoted.

□ The current postal address, telephone number, fax number, and **functioning email address** is provided for the corresponding author.

□ If an author has moved since the work described in the article was done, or was visiting at the time, a **"Present address"' (or "Permanent address")** may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes

Abstract

□ **Word count** limitations are observed.

□ For letters to the editor, an **abstract is not required**.

□ For original research reports and reviews, a **structured abstract** is required. The abstract must be divided into the following sections: Objective, Methods, Results, and Conclusions.

References

□ References are cited in text by **number in order of appearance**.

□ All references provided in the reference listing have been **cited within the text** of the manuscript.

□ References should be cited in the text by Arabic numerals in square brackets, [1], [2], etc., in order of appearance and follow the **Vancouver Style** (http://www.library.uwa.edu.au/education_training_and_support/guides/citing_your_sources_-_vancouver_style). Only articles that have been published or are in press should be included in the references. Unpublished results or personal communications should be cited as such in the text.

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Tables and Figures

□ **Table and figure limitations** are observed. Any excess tables or figures are supplied as supplementary materials.

□ Please see http://www.elsevier.com/artworkinstructions for **additional instructions**

□ All figures are provided in EPS, TIFF, JPEG, or PDF **file format** and all tables are provided in DOC or RTF file format.

□ All figures pass system **quality check** on the "QC Check" screen and are provided in high resolution.

□ All tables and figures are **labeled and files are named** according to the order of appearance in the manuscript.

□ Each table or figure has an **accompanying legend**. Labels on legends should match labels on figures or tables. All table and figure legends should be provided in a list in the order of appearance of citation within the manuscript text. This list should appear at the end of your

manuscript file (not in a separate file) after your reference listing. Please ensure that the label on each legend matches the label on the corresponding figure. Legends for supplementary figures should be labeled “S1”, “S2”, etc.

□ Neither tables nor figures are embedded in the manuscript text. Figures should be provided in a **separate file**, while tables may be presented either in a separate file or at the end of your manuscript file.

□ All figures and tables are **readable and appear in full** in the system built PDF. Nothing should be cut off from the edge of the page or be otherwise unreadable.

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Article draft for Gynecologic Oncology

Sexual function in cervical cancer patients after radiation therapy: a systematic review

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<To be revised before submitting for publication>

Abstract

Objective: Cervical cancer (CC) has a low mean age world-wide, and it is today a known fact that many of these women undergoing a number of different treatment modalities including radiotherapy for their disease may develop a decreased sexual health. The purpose of this systematic review was to asses the effect of radiotherapy on sexual function in women treated with radiotherapy for their cervical cancer.

Methods: A systematic review was performed on English-language articles dated from 1993 and the search was performed until august 2012. Searches identified and included both cross-sectional and cohort studies though MEDLINE, EMBASE, CINAHL and SveMEd+ databases. Methodological quality where assessed using checklists recommended by The Norwegian Knowledge Centre for Health Services (NOKC). Meta-analysis' were performed using Review Manager 5.

Results: Nine observational studies with controls where eligible for the systematic review, with the total of 1635 participants. Meta-analysis showed that women treated with radiotherapy for their cervical cancer had a significant greater risk for developing dyspareunia (Relative Risk, RR, 4.37), narrow/short vagina (RR 5.99), vaginal dryness (RR 3.04) and decreased sexual interest (RR 1.43) compared to healthy controls. When comparing the same four outcome-measures with women treated with surgery only as a control group, only dyspareunia (RR 1.36) where found to be significantly higher compared to control.

Conclusions: Results from this review suggests that there is some evidence that radiotherapy could cause a decreased sexual functioning in women treated for cervical cancer. Further studies are needed in this field, because patients will more and more relate to health-care as a product and demand that late-effects and rehabilitations of these be put on the agenda. Sexuality will always be important on the subjective level and it would be beneficial to make use of better inquiry-models that involves both qualitative and quantitative scientific methods.

Introduction

About 300 women are diagnosed with cervical cancer in Norway each year, and worldwide, this type of cancer is ranking as number two of types of cancer affecting women [1]. Worldwide, cervical cancer is also the most common cancer diagnosis that affects women under thirty-five years old, and it is a known fact that this diagnosis has a low mean age [1]. With increased access to early diagnosis, with screening and new modalities of treatment, the number of women surviving is increasing, at least in the Western part of the world [2-4]. Combinations of surgery (S), chemotherapy (CT), radiation (RT) have in the last years significantly improved women's chances of survival [5, 6].

Women who survive their cervical cancer may live with late-effects from disease and treatment for years, and studies conducted in the last two decades show that 30 to 60 % of women treated for cervical cancer experience late-effects such as sexual problems and decreased sexual functioning. This is especially relevant to those women treated with radiotherapy [7-9].

Adverse effects from radiation can occur for years after treatment, and may include scarring of tissue, dryness of the vagina, vaginal fistula and atrophies, shortness or narrowness of the vagina, hormonal dysfunctions, bleeding and pain with intercourse [8, 10]. In addition to this a lot of women struggle with problems related both to the small and the large intestines, as a cause of high doses of radiation [11, 12].

How diagnosis and treatment will affect a woman's sexual health is a problem that is issued through all phases of life, at all ages, regardless of sexual orientation, and whether or not one has a partner [13]. Women's sexuality has in a historical view been linked to taboo and feelings of shame. This might be an indicator for why the diagnosis of cervical cancer has been linked to the same. This is an important issue to put focus on, when health workers silence around subjects as sexual health and function are maintaining the ideas and existing myths related to cancer and sexuality. Barriers' resulting in failed communication about this subject is not making patients' problems with sexual function and dysfunction any smaller [14].

The main aim of this study was to present a systematic review of studies that examine sexual functioning in patients treated with radiotherapy for cervical cancer. The secondary aim is to review the studies included concerning design, methodology and outcomes, and from there discuss the quality of the published findings. The purpose of the study is to create more intelligibility about a subject many health workers neglect, and thereby also create a more unsafe setting for patients that want more information and openness around sexual functioning and sexuality.

Methods

Inclusion criteria

Criteria for inclusion and keywords for a systematic literature search where discussed with both senior methodologist and research librarian. The following criteria where set to be included in the systematic review: (1) Articles based on cross-sectional (C) or cohort studies (COH). (2) Articles that assessed sexual functioning as an adverse effect in adults with cervical cancer post radiotherapy-treatment; or studies, (C or COH), that had a mixed sample of patients, but where cervical cancer patients could be identified in the results. (3) Articles that presented the time-frame used when conducting measurements in the patient group(s). (4) Articles published in Norwegian, Danish, Swedish or English.

Identification of literature

Electronic strategies were developed in-team, in consultation with librarians with experience of performing systematic reviews. Search strategies included terms; "cervix cancer", "cervical cancer", "cervix neoplasm", "cervical neoplasm", uterine cervical neoplasm", "radiotherapy (adverse effects, complications)", "radiation injuries", "sexual function/dysfunction (physiological)", sexual morbidity", "sexual behaviour", "sexual partners", "sex counselling" and "sexual and gender disorders".

Searches of literature were conducted in Medline/Pubmed, CINAHL, EMBASE and SveMEd+. Electronic searches were first conducted in October 2011 then updated several times, lastly in September 2012. Electronic searches were supplemented by hand searches of reference lists of papers meeting inclusion criteria and relevant reviews identified through the electronic searches.

Selection of articles

The selection of articles was conducted by two reviewers. Firstly, all abstracts where read through and those irrelevant due to either wrong study design or irrelevant population were excluded. Secondly, all articles where reviewed after the inclusion criteria, and studies that did not meet the intended criteria where excluded. Full text reports of studies that were potentially meeting the inclusion criteria were provided in full text. Some questions concerning study design came up in the process of selection, but were resolved between the two reviewers. Further information was requested from authors of two papers of whom none responded, and no additional information on their papers was provided. See figure 1 for a summary of the study selection process.

Data extraction

Data was retrieved from the selected articles by one reviewer and approved by the secondary reviewer. Data retrieved were first collected in a reading-matrix used as a tool for analyzing text and data. Details of participants, measure and settings were collected from the reading-matrix and presented in Table 1.

Methodological quality assessment of studies

Studies included in the review were methodologically assessed using quality assessment tools for cross-sectional and cohort studies, recommended by The Norwegian Knowledge Centre for Health Services [15] (See attachments). Quality was assessed by the two reviewers independently with consensus being reached on discussion where discrepancies in assessments were found. Studies were given scores according to their quality; high, moderate or low. Maximum scores for cross-sectional studies were 7 points and for cohort studies 10 points. Issues or criteria were addressed by yes, no or unclear, and only yes would actually

result in a point. A high score indicates that all criteria from the checklists used are fulfilled. A moderate score is given if most of the criteria of the protocol used are met, but where some criteria are missing or inadequately described by author(s). Then again, it is considered unlikely, that these unfulfilled or missing criteria will significantly alter the final conclusion of the systematic review. A low score is applied if very few or none of the used protocols criteria are met. It is considered likely or very likely that these inadequately described or missing criteria will significantly change the final conclusion of the systematic review [15].

Analyses

Parts of the data in this systematic review are presented in tables and are analysed and described in narrative tradition. This is because of the heterogeneity found in measures and outcome. Where it was possible, outcomes related to sexual functioning are presented in meta-analyses. The meta-analyses performed, where conducted using Review Manager 5. Because of expected highly measured heterogeneity within the outcomes, it was determined to use the random effect model (RE). Heterogeneity among studies was assessed using I^2 statistic.

The dichotomous measure risk-ratio (RR) where measured for each one of the outcomes. The risk-ratio is found by dividing the absolute risk for the exposed group, by the absolute risk of a control group [16]. Risk-ratio is here used to determine the probability of the occurrence of an event in one group “radiotherapy” relative to another group “healthy control” or “surgery”. Studies were compared even though they made use of different instruments for measuring sexual functioning. It was also decided to include both cross-sectional studies and cohorts into the meta-analysis. In cases where follow-up data where collected over a large period of time, it was determined to use data collected closest to 12 months if possible to maximize consistency across studies.

Results

Literature search in electronic data-bases and hand-searching identified 120 articles as seen in the flow diagram below. 103 of these references were excluded from the project due to study-designs and/or irrelevant populations. Only 17 of the articles found were included for further quality assessment. Further 8 references were excluded because of low methodological quality or they did not meet the criteria set for inclusion (Figure 1). 9 studies, (3 cohorts and 6 with a cross-sectional study-design), were included in this study [7-10, 17-21]. The studies provided information from the total number of 1635 patients.

Among the cohort studies one was produced in The Netherlands [21], while two articles were produced in Denmark [9, 19], based on the same patient population. Among the cross-sectional studies one were produced in Sweden [10], one in Scotland [7], two in the USA [8, 17], and the reminding two articles were produced in Austria [18] and South-Korea [20]. Characteristics of the studies included in the review, and features used for quality assessment are illustrated in Table 1.

Figure 1: Flow diagram over identified literature

Table 1: Studies included in review (alphabetical order), and characteristics used for quality assessment

Methodological quality assessment of studies included

Methodological quality was assessed using checklists [15](see attachements). Details of the methodological quality of studies are presented in Table 2 and 3. All of the three cohorts scored high in the quality assessment, whereas among the cross-sectional studies, three scored moderately and three scored high.

Table 2: Methodological quality assessment: Cross-sectional studies sexual function in women after radiotherapy for cervical cancer

Table 3: Methodological quality assessment: Cohort studies on sexual function in women after radiotherapy for cervical cancer

The most common shortcoming in methodology among the cross-sectional studies was whether or not a description was made of differences in respondents vs. non-respondents. This was not found in two of the studies included, and it was deemed unclear if it was done in another two. The most common shortcoming among the cohorts was if there occurred a blinded outcome assessment or not.

Measure of sexual function in the articles included in the systematic review

Bergmark et al. [10] used a self-made questionnaire in their study that consisted of 136 questions for women with cervical cancer and 115 questions for the healthy controls. The questionnaire was designed to map out symptoms of sexual dysfunction as; reduced sexual interest; changes in sexual response; changes in length and elasticity of the vagina; dyspareunia and frequency of intercourse, orgasm and sexual pleasure. Informants were asked to describe every symptom they have/had experienced (frequency, intensity, time-length and quality), and also respond to in what grade they were stressed out over each symptom.

Cull et al. [7] also made use of a self-made questionnaire to measure sexual relations/functioning. Sexual interest and activity were measured on a 7 point scale (never - daily). 7 parts of the questionnaire measured sexual response and pain with a 5 point scale (never – usually). Since this study was a retrospective cross-sectional study, data described the women's sexual function today (time of measurement) and retrospectively what the women thought their sexual function was before time of diagnosis.

In the study conducted by Donovan et al. [17] several validated questionnaires with good internal consistency were used to measure sexual functioning. Sexual health was measured with the Sexual Function – Vaginal Changes Questionnaire (SVQ). SVQ measures sexual and vaginal problems, as well as sexual satisfaction in patients with gynaecological cancers. To measure sexual interest and sexual dysfunctions the authors made use of sub-scales of the Cancer Rehabilitation Evaluation System (CARES). Relationship with partner(s) was measured with The Dyadic Adjustment Scale (DAS), which consists of 32 parts that measures satisfaction, consensus, and cohesion and affection expression.

The Sexual self-schema (SSSW) was used to measure women's cognitive generalizations about sexual aspects in themselves. Passionate – romantic, open – direct and embarrassed – conservative was calculated by summarizing the different parts of the questionnaire [17].

Frumovitz et al. [8] made use of the Menopausal Survey and the Female Sexual Function Index (FSFI) to calculate menopause and measure symptoms related to sexual functioning. The survey consists of 19 items covering sexual desire, arousal, lubrication, orgasm, satisfaction and pain. To measure treatments impact on social relationships The Abbreviated Dyadic Adjustment Scale (A-DAS) was used on women in a serious relationship of six months or more and The Cancer Rehabilitation Evaluation System (CARES) was used on single women.

Greimel et al. [18] used The European Organisation for Research and Treatment of Cancer (EORTC) Cervix Cancer Module (QLQ-CX24). The questionnaire consists of three scales with multiple parts (experience of symptoms, body-image and sexual functioning) and five independent scales (lymphedema, lower back pain, menopausal symptoms, "tickling" sensations, numbness and sexual satisfaction). The Sexual Activity Questionnaire (SAQ) was used to measure sexual activity, pleasure and pain. The questionnaire is divided into three different sections were section 1 measures if the women is sexually active or not, section 2 look for reasons for sexual inactivity and section 3 measure sexual function for women responding to being sexually active. Section 3 consists of 10 questions about sexual pleasure, pain and sexual habits/frequency. The Pleasure-scale measures from 0-18 were a low score indicates less sexual pleasure. The Pain-scale measures from 0-6 were a low score indicates more pain related to sexual situations. Habits and frequency measures from 0-3 were 0=less than usually and 3=more than usually.

Jensen et al. [9] used Sexual Function-Vaginal Changes Questionnaire (SVQ), were 7 of the 27 parts the questionnaire consists of were used to evaluate grade of sexual function and vaginal changes compared to pre-diagnosis and was designed for longitudinal studies. The questionnaire includes five main areas related to female sexual dysfunction: Sexual interest, lubrication, orgasm, pain and overall sexual satisfaction. In addition to these areas it also covers vaginal problems, partner-issues; sexual issues in general, intimacy and body-image.

The Uro-Gynecological Morbidity Questionnaire was designed to map out patients own experience with gynaecological and urological symptoms after treatment for gynaecological cancers [9].

Klee et al. [19] made use of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 to measure general quality of life and supplemented this questionnaire by a self-made questionnaire measuring symptoms divided into gastro-intestinal, urological and gynaecological areas.

Park et al. [20] made use of The European Organisation for Research and Treatment of Cancer (EORTC) Cervix Cancer Module (QLQ-CX24) to measure sexual function in their study. The survey covers symptom experience, body image and sexual and/or vaginal functioning. The National Health and Social Life Study (NHSLS) which studies sexual behaviour and problems in the general adult population were also used to measure sexual health and problems related to this issue.

Pieterse et al. [21] made use of the Leiden Questionnaire (LQ) for measuring sexual function in their study. The questionnaire consists of 14 parts where 9 measure sexual function. Questions about sexual functioning were answered in Likert-scales of 3, 4 or 5 points. For analysis, all these scales were made dichotomous.

Meta-analysis

Dichotomous data eligible and relevant to this study on sexual functioning were found in four out of nine studies included [9, 10, 20, 21]. Dichotomous data will be presented in a meta-analysis on four different outcomes (dyspareunia, narrow/short vagina, vaginal dryness and sexual interest) that are related to women's sexual functioning. Where it was considered possible, meta-analysis was conducted on both women treated with radiotherapy for their disease versus healthy controls and versus women who where treated surgically. The dichotomous measure risk-ratio (RR) was summarized for each one of the outcomes.

Dyspareunia – Pain with intercourse

The most used definition of dyspareunia is genital pain before, during or after sexual intercourse [22].

In the analysis showing RR for dyspareunia, there is a significant difference in pain with intercourse for women that have undergone radiotherapy for cervical cancer compared to healthy controls. In the overall measured RR as seen in Figure 2, women with cancer have a significant greater chance of experiencing pain with intercourse than the healthy controls do, RR 4.37 (95% CI 1.39 – 13.78). The effects of the independent studies are presented in the forest plot (Table 3). The radiotherapy group consists of patients who have received either only radiotherapy or surgery and radiotherapy combined. The p-value of overall effect here also supports the significant findings with P=0.01. Effect of individual studies were heterogeneous (I^2 =79%).

Figure 2: Relative Risk for dyspareunia Radiotherapy vs. Control

In the analysis measuring RR for dyspareunia in women treated with radiotherapy for their cervical cancer versus women treated with only surgery (Figure 3), only two articles where summarized. Summarizing the two studies in Figure 3, show that women treated with radiotherapy have a somewhat greater chance, of experiencing dyspareunia than women treated with surgery only, RR 1.36 (95% CI 1.14-1.64). In Pieterse' study from 2006, the confidence interval encloses 1, but the overall effect shows a small significant difference (P=0.0008) between women treated with radiotherapy and women treated surgically.

Figure 3: Relative Risk for dyspareunia Radiotherapy vs. Surgery

Narrow/Short Vagina

The analysis on narrow/short vagina (Figure 4), shows that patients treated with radiotherapy, scored significantly worse than the healthy controls. All of the studies included found significant differences between radiotherapy and controls, and in the overall measured RR it was found that women treated with radiotherapy have a significant higher chance of developing narrow or short vagina than controls have, RR 5.99 (CI 95% 3.13-11.48). This

finding is also supported by the overall p-value of 0.00001. Effect of individual studies were heterogeneous (I^2 =39%).

Figure 4: Relative risk for narrow/short vagina Radiotherapy vs. Control

When summarizing radiotherapy vs. surgery (Figure 5), no significant differences where found between women treated with radiotherapy and women treated surgically when measuring RR for experiencing narrow or short vagina, RR 1.45 CI 95% 0.90-2.33). The 95% confidence interval encloses 1 and the P-value is also considered insignificant.

Figure 5: Relative risk for narrow/short vagina Radiotherapy vs. Surgery

Vaginal Dryness

The outcome of vaginal dryness (Figure 6) were also, as found within all of the studies included, significantly worse for patients than for healthy controls, RR 3.04 (CI 95% 1.85-5.00) (P=0.0001). Effect of individual studies were heterogeneous (I^2 =70%).

Figure 6: Relative Risk for vaginal dryness Radiotherapy vs. Control

No significant differences where found when measuring the RR for vaginal dryness between women treated with radiotherapy and women treated with only surgery in Figure 7, RR 1.06 (CI 95% 0.90-1.25). All 95% confidence intervals enclosed 1 and the P-value was also considered insignificant.

Figure 7: Relative Risk for vaginal dryness Radiotherapy vs. Surgery

Sexual Interest

In the analysis for sexual interest seen in Figure 8, it was found that the healthy control group had a significantly (P=0.004) better overall score than women treated with radiotherapy RR 1.43 (CI 95% 1.12-1.83). Effect of individual studies were heterogeneous (I^2 =81%).

Bergmark 1999 was the only study included that did not find any significant differences between patients and controls on this outcome, and this may represent some of the heterogeneity found.

Figure 8: Relative risk for sexual interest Radiotherapy vs. Control

No significant differences where found between radiotherapy and surgery groups when measuring RR for sexual interest shown in Figure 9, RR 1.06 (CI 95% 0.93-1.20). The confidence intervals for all three studies summarized enclosed 1 and the P-value in this meta-analysis was also determined insignificant.

Figure 9: Relative risk for sexual interest Radiotherapy vs. Surgery

In this study, it was not possible to include every article into meta-analysis. This due to the lack of dichotomous data needed to be analysed. Data collected in these articles concerning aspects on sexual health showed the same tendency as the results from studies included in the meta-analyses with women with cervical cancer having deteriorated sexual functioning after treatment, also compared to healthy controls. Studies from Cull et al. and Frumovitz et al. found that irradiated women reported significantly more problems with dyspareunia compared to women who had surgery only or to healthy controls [7, 8]. Greimel et al. found that having a narrow/short vagina was a significantly larger problem for irradiated women than any of the other treatment groups or healthy controls [18]. Results from Cull et al. showed that vaginal dryness was a significant problem for women treated with surgery, radiotherapy or both [7]. Frumovitz et al. found that vaginal dryness was a large problem for irradiated women [8]. Three studies all issued the reported problem of lower sexual interest and/or activity for all patients treated for cervical cancer [7, 17, 18]. Sexual functioning data from all studies that are not included in the meta-analysis are summarized in Table 4.

Discussion

Nine studies where eligible for the systematic review, three cohort studies and six cross-sectional studies (1993-2008). All the studies scored moderate or high in methodological criteria. The follow-up time in the studies included ranges from average 97 weeks to average 70 months, with number of participants from 50 to 860. Meta-analysis showed that women treated with radiotherapy for their cervical cancer had a significant greater risk for developing dyspareunia, narrow/short vagina, vaginal dryness and decreased sexual interest compared to healthy controls. We chose to include surgical patients as a control group in the meta-analysis because it could give an indication to if radiotherapy as a treatment in itself were causing these outcomes or if the whole treatment for cervical cancer causes the adverse effects seen. Meta-analysis performed on the same four outcome-measures show that only dyspareunia were significantly greater for women treated with radiotherapy compared with women treated with surgery only.

In this review, a systematic approach has been taken to avoid bias when including studies, by using validated checklists and a reading-matrix for each and every study included. Although the studies clearly, since a large part of them are greater QoL-studies, measure more than sexual function and health, this is what this master thesis is focusing on, and thereby only reporting from.

Including meta-analysis in a systematic review offers a wide range of challenges. In studies included there is variation in study designs, size and disease stages of patient populations, instruments used for measure and treatment-regimes; in other words clinical and methodological heterogeneity. Making liberal choices when it comes down to patient and treatment criteria can make results difficult to analyze and compare. For the most part it became clear that the dichotomous data found was not able to clearly single out only radiotherapy as treatment, or it was possible in some cases, but would simply make the patient-group to small for a comparison. Meta-analysis is based on patients who received radiotherapy of some kind and/or surgery vs. healthy controls or patients who received surgery only. It was decided to use the “combined” group in this study, because of the fact that most women seeking medical help for cervical cancer are introduced to a multi-modality

treatment, including both surgery and radiotherapy [6, 23-25]. This can clearly be regarded as a bold choice to make and it could be discussed whether or not data should have been combined. On the other hand, in the meta-analysis conducted on Radiotherapy vs. Surgery, no significant differences were found in this study between treatments expect for dyspareunia, even though surgery only could implicate an earlier stage if disease [26].

One should always realize the bias that may occur with the use of subjective questionnaires. Measuring late-effects on patients, their reporting could be influenced by what we call "response-shift" after treatment. Human beings have their own ability to change their expectations in line with how reality works. Many patients end up with changing their perspective on sickness and life in general, and manage to adapt or cope with their new life-situation after treatment [27, 28]. Here in this review, the studies measured outcomes where considered more reliable if the instruments used to measure where validated.

In relation to the possibility of publication bias, hand-searching after reference-lists was conducted during data-collection, but no approach was taken in this systematic review on searching for unpublished data outside of the databases mentioned above. One should be aware of the bias of period effect when conducting a systematic review, and although all of the studies included are fairly new ones, data in some of them have been collected over years, and thus it is very possible that regimes of cancer treatment have changed [16, 29]. Although the results from the meta-analysis conducted here by no mean reflect this, it is for example a known fact that the use of adjuvant chemotherapy (Cisplatin) with radiotherapy have been introduced and increased over the last 15 years [20, 30, 31].

To our knowledge, very few studies have conducted this kind of a meta-analysis in published literature in sexual functioning in women after radiotherapy-treatment for cervical cancer. Our overall effect findings show that women treated with radiotherapy for cervical cancer have a significantly higher risk of developing vaginal dyspareunia, vaginal dryness, narrow/short vagina and reduced sexual interest compared with women from a healthy norm. We also conducted an analysis between women treated with radiotherapy for their cancer and those women treated with surgery only. Here the results indicate that only the risk for developing pain with intercourse, dyspareunia, where significantly different between the two groups, as women treated with radiotherapy scored worse.

The four outcome-measures included here and the result of them compared to healthy controls, are comparable to results from other studies on women's sexual health and satisfaction after gynecologic cancers [7, 8, 17-19, 32-36]. It is hard though, to conclude that radiotherapy alone is the cause of adverse effects of treatment after cervical cancer. A high heterogeneity indicates differences in disease-stages, populations and treatments, and there are overall few patients in this study.

Dyspareunia, pain with intercourse, was the only outcome that women treated with radiotherapy had a significant risk of developing compared to surgery only. This also indicates that surgery could cause parts of the treatment-effects patients are experiencing. According to several articles on sexual functioning, dyspareunia can be linked with other measured outcomes in this study. In addition to surgery often being the primary given treatment with narrowing scar-tissue as a late-effect, secondary treatment irradiation may damage the vaginal mucosa permanently, and could lead to fibrosis which again can cause more narrowing og shortness of the vagina [23, 37]. A narrow/short vagina and thin mucosal wall may lead to pain and bleeding during penetration. Surgery and/or high doses of radiation may also cause damage to the ovaries and lead to lack of estrogen, which again contributes to lack of lubrication (vaginal dryness) and leads to dyspareunia [23, 37].

The research on assessing women's sexual functioning after cervical cancer is a work in progress. One can only hope that there comes a future where women's sexual health issues are regarded with the same importance as for example men's sexual issues after prostate cancer. Possible interventions done to help women's sexual functioning should be based solely on female responses after pelvic radiation and it would be beneficial if women's sexuality was regarded in a more holistic way. Sexuality is a subjective matter and it would be valuable if further studies in this field would make use of both the quantitative and the qualitative methods. Further studies in this field would be of significance for both health workers and the future patients as they also give a pin-point at what should be communicated to patients about late-effects before they start their treatment-regime.

Conflict of interest

We declare that we have no conflicts of interest.

Abbreviations

A-DAS=The Abbreviated Dyadic Adjustment Scale; BDI= Beck Depression Inventory; BSI-18=Brief Symptom Index-18; BSRQ-PAE=The Body-Self Relations Questionnaire – Physical Appearance Evaluation subscale; C=Cross-sectional study; CARES=Cancer Rehabilitation Evaluation System; CI=Confidence interval; COH=Cohort study; CT=Chemotherapy; DAS=The Dyadic Adjustment Scale; EORTC QLQ-C30=The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; FSFI=Female Sexual Function Index; LQ=Leiden Questionnaire; NHSLS=The National Health and Social Life Survey; QLQ-CX24=The European Organisation for Research and Treatment of Cancer, Cervix Cancer Module; RE=Random effect; RR=Risk Ratio; RT=Radiotherapy; RSCL=The Rotterdam Symptom Checklist; S=Surgery; SAQ=Sexual Activity Questionnaire; SF-12=Short Form-12; SSSW=The Sexual Self-schema Scale for Women; STAI=Spielberger State Trait Anxiety Inventory; SVQ=Sexual function – Vaginal changes Questionnaire.

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Figures

Figure 1: Flow diagram over identified literature

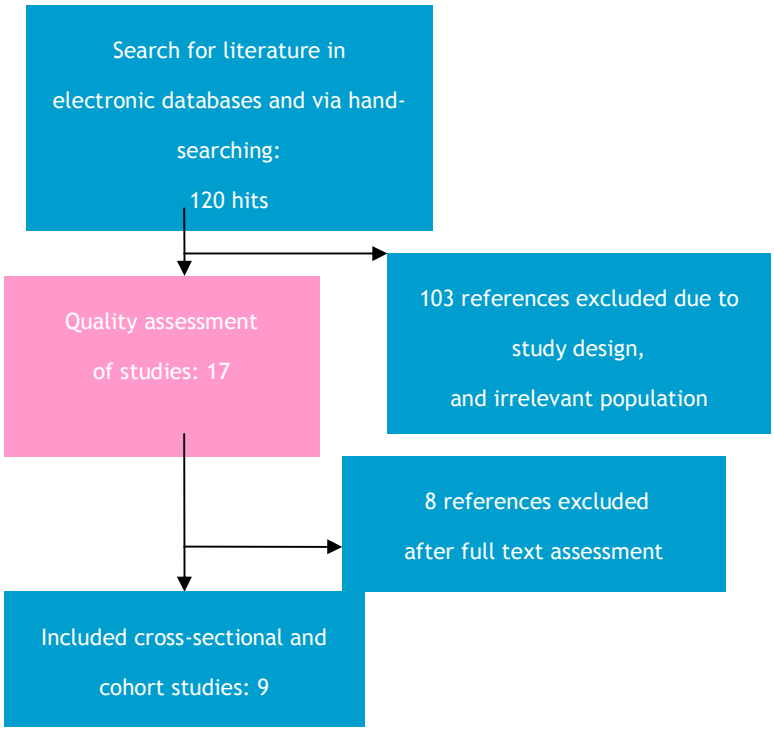


Figure 2: Relative Risk for dyspareunia Radiotherapy vs. Control

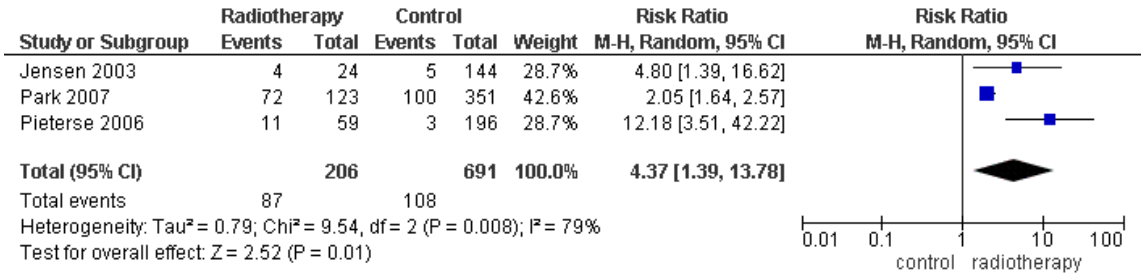


Figure 3: Relative Risk for dyspareunia Radiotherapy vs. Surgery

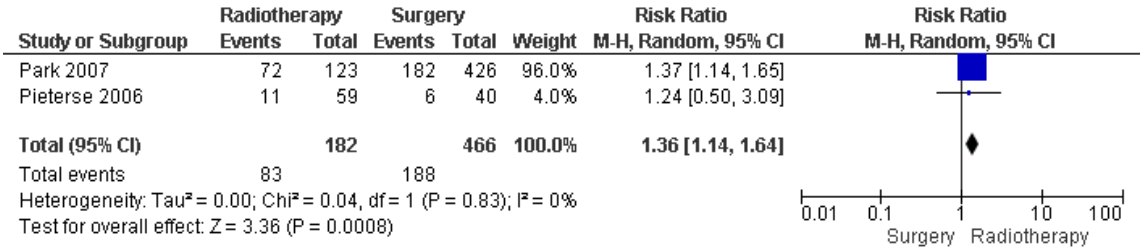


Figure 4: Relative risk for narrow/short vagina Radiotherapy vs. Control

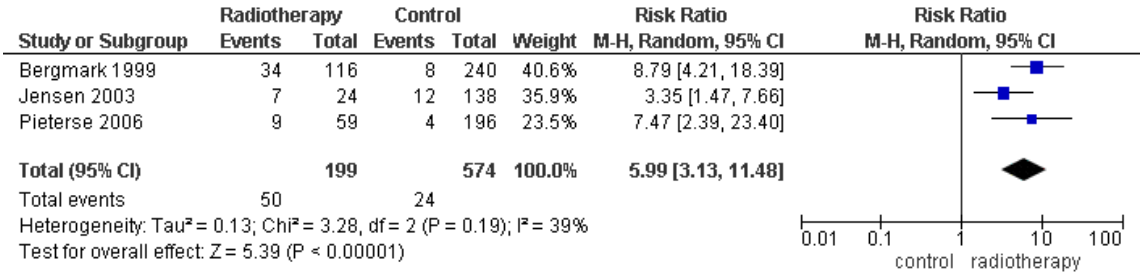


Figure 5: Relative risk for narrow/short vagina Radiotherapy vs. Surgery

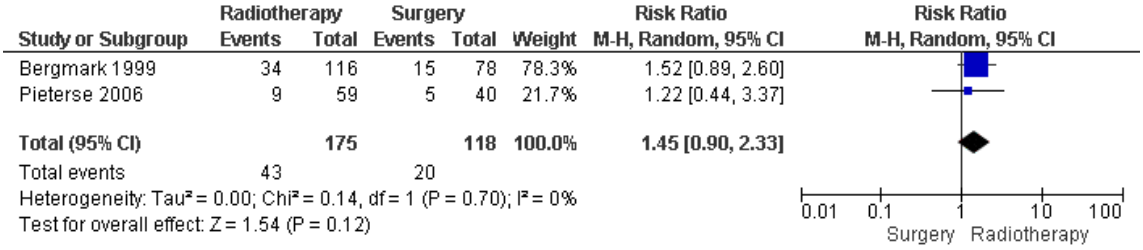


Figure 6: Relative Risk for vaginal dryness Radiotherapy vs. Control

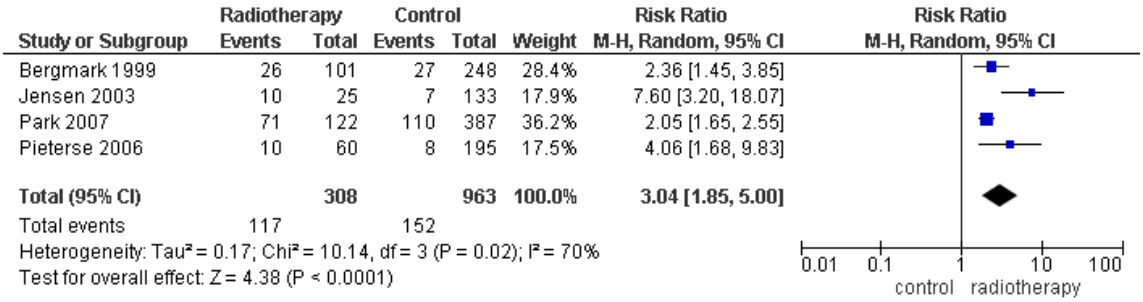
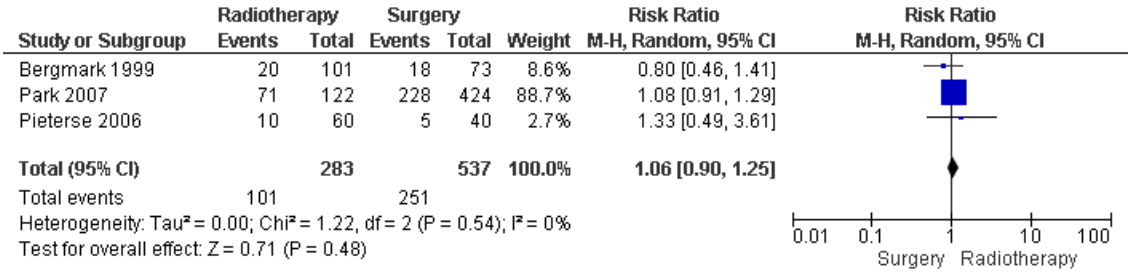


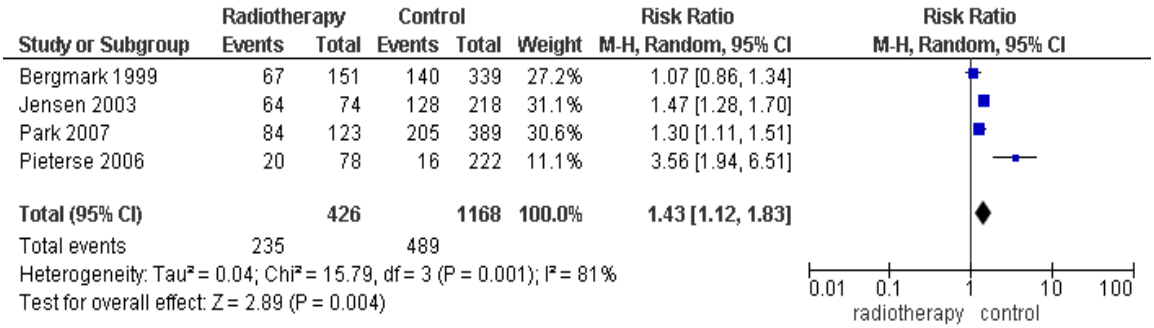
Figure 7: Relative Risk for vaginal dryness Radiotherapy vs. Surgery



Study or Subgroup	Radiotherapy Events	Total	Surgery Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bergmark 1999	20	101	18	73	8.6%	0.80 [0.46, 1.41]
Park 2007	71	122	228	424	88.7%	1.08 [0.91, 1.29]
Pieterse 2006	10	60	5	40	2.7%	1.33 [0.49, 3.61]
Total (95% CI)		**283**		**537**	**100.0%**	**1.06 [0.90, 1.25]**
Total events	101		251			

Heterogeneity: Tau² = 0.00; Chi² = 1.22, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)

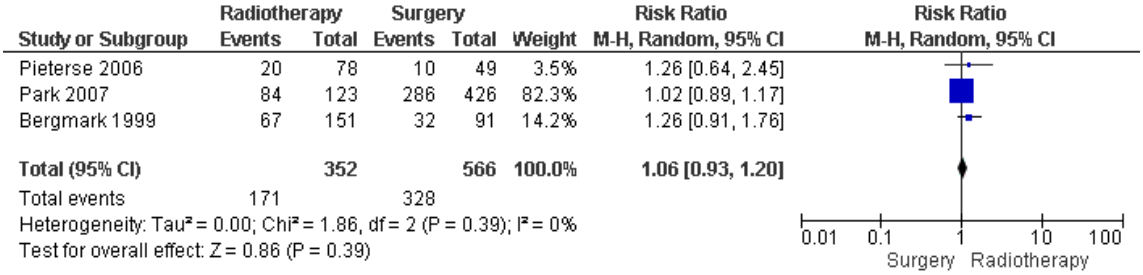
Figure 8: Relative risk for sexual interest Radiotherapy vs. Control



Study or Subgroup	Radiotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bergmark 1999	67	151	140	339	27.2%	1.07 [0.86, 1.34]
Jensen 2003	64	74	128	218	31.1%	1.47 [1.28, 1.70]
Park 2007	84	123	205	389	30.6%	1.30 [1.11, 1.51]
Pieterse 2006	20	78	16	222	11.1%	3.56 [1.94, 6.51]
Total (95% CI)		**426**		**1168**	**100.0%**	**1.43 [1.12, 1.83]**
Total events	235		489			

Heterogeneity: Tau² = 0.04; Chi² = 15.79, df = 3 (P = 0.001); I² = 81%
Test for overall effect: Z = 2.89 (P = 0.004)

Figure 9: Relative risk for sexual interest Radiotherapy vs. Surgery



Study or Subgroup	Radiotherapy Events	Total	Surgery Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Pieterse 2006	20	78	10	49	3.5%	1.26 [0.64, 2.45]
Park 2007	84	123	286	426	82.3%	1.02 [0.89, 1.17]
Bergmark 1999	67	151	32	91	14.2%	1.26 [0.91, 1.76]
Total (95% CI)		**352**		**566**	**100.0%**	**1.06 [0.93, 1.20]**
Total events	171		328			

Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 2 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)

Tables

Table 1: Studies included in review (alphabetical order), and characteristics used for quality assessment

Author	N	Design	Measure	Disease stage (FIGO)	Treatment and outcome measured for meta-analysis (where possible)	Time frame
Bergmark et al., 1999	256	C	Self-made	Ib-IIa	S or RT or both Narrow/short vagina Vaginal dryness Sexual interest	>60 months
Cull et al., 1993	83	R-C	RSCL, STAI, BDI, self-made	Ib	S of RT or both	97 weeks*
Donovan et al., 2006	50	C	SVQ, sisd-CARES, DAS, SSSW, BSRQ-PAE	0-III	CT+RT or S or S+RT (CT)	36 months*
Frumowitz et al., 2005	74	C	FSFI, SF-12, BSI-18, A-DAS, CARES, Menopausal Survey	I	S or RT	<90 months
Greimel et al., 2009	121	C	EORTC QLQ-C30, QLQ-CX24, SAQ	I-IV	S or S+RT or S+CT	106 months[n]
Jensen et al., 2003	118	COH	EORTC QLQ-C30, SVQ, Uro-Gynecological Morbidity Questionnaire, self-made	Ib-IVa	RT Dyspareunia Narrow/short vagina Vaginal dryness	24 months
Klee et al., 2000	118	COH	EORTC QLQ-C30, Self-made, based on EORTC QLQ-C30	I-IVa	RT or RT+CT	24 months
Park et al., 2007	860	C	EORTC QLQ-C30, QLQ-CX24, NHSLS	I-IVa	S+CT or S+RT or S+RT+CT or RT or CT+RT Dyspareunia Vaginal dryness Sexual interest	70 months[n]
Pieterse et al., 2006	73	COH	LQ	I-IIa	S or S+RT Dyspareunia Narrow/short vagina Vaginal dryness Sexual interest	24 months

*=mean time since treatment
[n]=mean time since diagnosis

C: Cross-sectional study; COH: Cohort study; RT: Radiotherapy; S: Surgery; CT: Chemotherapy.
Measures: RSCL: The Rotterdam Symptom Checklist; STAI: Spielberger State Trait Anxiety Inventory; BDI: Beck Depression Inventory; SVQ: Sexual function – Vaginal changes Questionnaire; CARES: Cancer Rehabilitation Evaluation System; DAS: The Dyadic Adjustment Scale; SSSW: The Sexual Self-schema Scale for Women; BSRQ-PAE: The Body-Self Relations Questionnaire – Physical Appearance Evaluation subscale; SF-12: Short Form-12; BSI-18: Brief Symptom Index-18; A-DAS: The Abbreviated Dyadic Adjustment Scale; FSFI: Female Sexual Function Index; EORTC QLQ-C30: The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; QLQ-CX24: The European Organisation for Research and Treatment of Cancer, Cervix Cancer Module; SAQ: Sexual Activity Questionnaire; NHSLS: The National Health and Social Life Survey; LQ: Leiden Questionnaire.

Table 2: Methodological quality assessment: Cross-sectional studies sexual function in women after radiotherapy for cervical cancer

	Criteria*								
Study (cross-sectional)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Total/7**	**Quality**
Bergmark et al. 1999	+	+	-	+	+	?	+	5	Moderate
Cull et al. 1993	+	+	-	?	+	?	+	4	Moderate
Donovan et al. 2006	+	+	+	+	+	+	+	7	High
Frumovitz et al. 2005	+	+	?	?	+	+	+	5	Moderate
Greimel et al. 2009	+	+	?	+	+	+	+	6	High
Park et al. 2007	+	+	+	?	+	+	+	6	High

Note: + = yes, - = no, ? = unclear.

*Following issues where addressed by the checklists used (for cross-sectional studies): 1) Defined population, 2) population representative, 3) description of differences in respondents vs. non-respondents, 4) adequate response rate, 5) standardized collection of data, 6) reliable outcome measurements, 7) adequate methods used in data analysis.

Table 3: Methodological quality assessment: Cohort studies on sexual function in women after radiotherapy for cervical cancer

	Criteria*											
Study (cohort)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Total/10**	**Quality**
Jensen et al. 2003	+	+	+	+	+	+	+	+	+	?	9	High
Klee et al. 2000	+	+	+	+	+	?	+	+	+	?	8	High
Pieterse et al. 2006	+	+	+	+	+	+	-	+	+	?	8	High

Note: + = yes, - = no, ? = unclear.

*For cohort studies: 1) Exposed group and non-exposed group comparable, 2) exposed informants' representative for a population, 3) non-exposed group chosen from the same population as the exposed individuals, 4) prospective study, 5) reliable and equal outcome measurements for both groups, 6) adequate amounts of individuals in the cohort, 7) dropout analysis, 8) long enough follow-up time to prove negative and/or positive outcomes, 9) possible confounders taken into account in study design and/or analysis, 10) blinded outcome assessment.

Table 4: Reported outcomes in articles not included in meta-analysis and data supporting them

Author	Treatment	Outcome	Result
Cull et al., 1993	S of RT or both	Fatigue Depression/anxiety Functional status *Pain with intercourse* *Sexual pleasure/enjoyment*	Fatigue was a moderate to severe problem for about 33 % of the patients as a group (both surgery and RTs), depression 22 % of the group. Ca 25% of all the patients reported reduced functional status. About 50% of the patients felt like their sexual function had deteriorated. (Interest, frequency of intercourse, arousal, lubrication, pain, enjoyment (P<0.005). RT patients reported significantly more often dyspareunia (P<0.01) and loss of sexual pleasure (P<0.01).
Donovan et al., 2006	CT+RT or S or S+RT (CT)	Sexual Health : *Sexual interest* *Sexual dysfunction* *Sexual satisfaction*	Patients had significantly worse sexual health than the control group. (Loss of sexual interest, more sexual dysfunction and less sexual satisfaction). Significantly more sexual dysfunction for RT than women treated with surgery only.
Frumovitz et al., 2005	S or RT	Quality of life (QoL) Psychological distress Menopausal symptoms *Desire* *Arousability* *Lubrication* *Orgasm* *Satisfaction* *Pain* Relationship satisfaction	RT patients scored significantly lower than patients only treated with surgery and healthy controls in overall QoL and psychological health. RT patients had significantly higher score on overall menopausal symptoms compared to both surgery patients and healthy controls. Patients treated with RT had significantly worse overall sexual function than both surgery patients and controls. Irradiated women had problems concerning becoming sexually aroused, vaginal dryness, reaching orgasm and also achieving sexual satisfaction. Women treated with RT also reported significantly more dyspareunia than any of the other two groups. No significant differences where found between the 3 groups in relations to dating or committed relationships.

Greimel et al., 2008	S or S+RT or S+CT	QoL Sexual function: *Sexual activity/habits* *Sexual pleasure* *Sexual discomfort*	Surgery+RT patients had lower score on overall QoL compared to other treatment groups and healthy controls. They scored significantly worse on physical functioning, role functioning, cognitive and social functioning. Irradiated women also had significantly more problems with symptoms as frequent urination, leaking of urin and the feeling of having a tight vagina. Surgery+RT patients scored significantly lower in the sexual activity rate than the two other treatment groups (p=0.006). No statistically differences where found among the groups concerning sexual pleasure and sexual discomfort.
Klee et al., 2000	RT or RT+CT	QoL Frequent voiding Diarrhea Vaginal discharge Irritation	Tiredness, weakness and the need to rest was acute symptoms that declined after 3 months. The patients' physical form got better as time passed by with an all-time high at 18 months. The patients experienced frequent voiding as both an acute, (just after treatment), and a chronic side-effect two years after treatment. Those patients who experienced the symptom as an acute effect had an all-time high at 3 months after treatment. Diarrhea experienced by large part of the patients and this was no indication for having the symptom becoming chronic later on. The number of patients that initially had high levels of diarrhea, declined during the first 3 months. Vaginal discharge and irritation around the vagina returned to the same level as controls after treatment.

S – Surgery
CT – Chemotherapy
RT - Radiotherapy

Literature search

S1 **CINAHL**

Search History March 27, 2012

#	Query	Limiters/Expanders	Last Run Via	Results
S10	S3 and S8 and S9	Search modes – Boolean/Phrase	Interface – EBSCOhost Search Screen – Advanced Search Database - CINAHL	9
S9	S4 or S5 or S6 or S7	Search modes – Boolean/Phrase	Interface – EBSCOhost Search Screen – Advanced Search Database - CINAHL	24192
S8	S1 or S2	Search modes – Boolean/Phrase	Interface – EBSCOhost Search Screen – Advanced Search Database - CINAHL	9521
S7	(MH "Sexual Counseling")	Search modes – Boolean/Phrase	Interface – EBSCOhost Search Screen – Advanced Search Database - CINAHL	459
S6	(MH "Sexuality+) OR (MH "Attitude to Sexuality+)	Search modes – Boolean/Phrase	Interface – EBSCOhost Search Screen – Advanced Search Database - CINAHL	20183
S5	(MH "Sexual and Gender Disorders+")	Search modes – Boolean/Phrase	Interface – EBSCOhost Search Screen – Advanced Search Database - CINAHL	3836
S4	(MH "Sexual Dysfunction, Female+")	Search modes – Boolean/Phrase	Interface – EBSCOhost Search Screen – Advanced Search Database - CINAHL	1525
S3	(MH "Cervix Neoplasms+")	Search modes – Boolean/Phrase	Interface – EBSCOhost Search Screen – Advanced Search Database - CINAHL	5401
S2	(MH "Radiation Injuries+")	Search modes – Boolean/Phrase	Interface – EBSCOhost Search Screen – Advanced Search Database - CINAHL	1883
S1	(MH "Radiotherapy+)	Search modes – Boolean/Phrase	Interface – EBSCOhost Search Screen – Advanced Search Database - CINAHL	8148

S2 **Medline/PubMed**

#	Searches	Results	Search Type
1	exp Radiotherapy/	121658	Advanced
2	Radiation Injuries/	23045	Advanced
3	rt.fs.	144114	Advanced
4	*libido/	1139	Advanced
5	Uterine Cervical Neoplasm/	53391	Advanced
6	exp Sexual Dysfunction, Physiological/	21287	Advanced
7	exp “Sexual and Gender Disorders”/	32776	Advanced
8	sex/ or exp sexual behavior/	76534	Advanced
9	Sex Counseling/	751	Advanced
10	(or/1-3) and 5 and (or/6-9)	71	Advanced
11	limit 10 to (danish or english or norwegian or swedish)	59	Advanced

S3 **Embase**

#	Searches	Results	Search Type
1	exp radiotherapy/	349809	Advanced
2	radiation injuries/	44904	Advanced
3	rt.fs.	212157	Advanced
4	Uterine Cervical Neoplasms/	22811	Advanced
5	exp sexual dysfunction, physiological/	50562	Advanced
6	exp “Sexual and Gender Disorders”/	50562	Advanced
7	sex/ or exp sexual behavior/	130448	Advanced
8	sex counseling/	686	Advanced
9	(or/1-3) and 4 and (or/5-8)	30	Advanced
10	(sex* and (cervical or cervix) and (neoplas* or cancer* or tumor* or tumour*) and (radiat* or radiother* or Brachyther* or irradiat*)).ti.	12	Advanced
11	9 or 10	38	Advanced
12	from 11 keep 4, 13-14, 19, 21-23, 26, 38	9	Advanced

S4 **Checklists for methodological quality**

SJEKKLISTE FOR KOHORTSTUDIER		**Ja**	**Uklart**	**Nei**
1	**Var gruppene (de eksponerte og ikke-eksponerte i kohorten) sammenliknbare i forhold til viktige bakgrunnsfaktorer**?			
Kommentar:				
2	**Var de eksponerte individene representative for en definert befolkningsgruppe/ populasjon?**			
Kommentar:				
3	**Ble den ikke-eksponerte gruppen valgt fra den samme befolkningsgruppen/ populasjonen som de eksponerte?**			
Kommentar:				
4	**Var studien prospektiv?**			
Kommentar:				
5	**Ble eksposisjon og utfall målt likt og pålitelig i de to gruppene?**			
Kommentar:				
6	**Ble mange nok personer i kohorten fulgt opp?**			
Kommentar:				
7	**Er det utført en frafallsanalyse som redegjør for om de som har falt fra skiller seg fra dem som er fulgt opp?**			
Kommentar:				
8	**Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall?**			
Kommentar:				
9	**Er det tatt hensyn til kjente, mulige forvekslingsfaktorer (konfoundere) i studiens design/og eller analyse?**			
Kommentar:				
10	**Er den som vurderte resultatene (endepunktene) blindet for hvem som var eksponert og hvem som ikke var eksponert?**			
Kommentar:				

Samlet kvalitetsvurdering av studien (intern validitet):

Høy kvalitet Brukes hvis alle eller nesten alle kriteriene fra sjekklisten er oppfylt.3 Eventuelle svakheter kan ikke endre studiens konklusjon.

Middels kvalitet Brukes hvis noen av kriteriene fra sjekklisten ikke er oppfylt eller hvis kriteriene ikke er tilfredsstillende
beskrevet. Det antas likevel at det er liten sjanse for at svakhetene faktisk kunne ha endret studiens konklusjon.

Lav kvalitet Brukes hvis få eller ingen kriterier fra sjekklisten er oppfylt eller ikke er tilfredsstillende beskrevet. Svakhetene kan innebære at studiens konklusjon er gal.

SJEKKLISTE FOR KASUS-KONTROLLSTUDIER		Ja	Uklart	Nei
1	**Var kasus- og kontrollpersoner hentet fra sammenliknbare befolkningsgrupper?**			
Kommentar:				
2	**Er gruppene (kasus og kontroll) sammenliknbare i forhold til viktige forvekslingsfaktorer (konfoundere)?**			
Kommentar:				
3	**Er kasusgruppens tilstand tilstrekkelig beskrevet og/eller diagnosen validert?**			
Kommentar:				
4	**Er det tydelig at kontrollgruppen var fri for den aktuelle tilstanden?**			
Kommentar:				
5	**Har forfatterne tatt hensyn til viktige forvekslingsfaktorer i studiens design og/eller analyse?**			
Kommentar:				
6	**Er eksponering for fare/skade/tiltak målt og gradert på samme måte i kasus- og kontrollgruppen?**			
Kommentar:				
7	**Var den som målte eksposisjonen blindet mht. hvem som var kasus eller kontroll (og spiller det ev. noen rolle om forskeren var blindet eller ikke)?**			
Kommentar:				
8	**Var responsraten (svarprosenten) tilstrekkelig i begge grupper?**			
Kommentar:				

Samlet kvalitetsvurdering av studien (intern validitet):

Høy kvalitet Brukes hvis alle eller nesten alle kriteriene fra sjekklisten er oppfylt.3 Eventuelle svakheter kan ikke endre studiens konklusjon.

Middels kvalitet Brukes hvis noen av kriteriene fra sjekklisten ikke er oppfylt eller hvis kriteriene ikke er tilfredsstillende
beskrevet. Det antas likevel at det er liten sjanse for at svakhetene faktisk kunne ha endret studiens konklusjon.

Lav kvalitet Brukes hvis få eller ingen kriterier fra sjekklisten er oppfylt eller ikke er tilfredsstillende beskrevet. Svakhetene kan innebære at studiens konklusjon er gal.