

REVIEW ARTICLE

Scoping Review on Gonadal Effects in Patients with Pelvic Irradiation

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ABSTRACT

This scoping review aimed to review studies on gonadal effects and time of recovery post-irradiation, and the approaches taken to manage the condition. A literature search was performed via three directories and databases including PubMed, Cochrane Library and Google Scholar. A total of 41 articles fulfilled the inclusion criteria of the study. The study populations primarily involved rectal cancer and Hodgkin's lymphoma. In general, there were 65 % of cases reported in female involved ovarian failure and dysfunction, while 36.4 % of cases reported in male showed hypogonadism, as the side effects from pelvic irradiation. The most common interventions were pre-treatment interventions, such as ovarian transposition. However, information on the time of recovery was limited from these studies. The review shows that more evidences exist for the potency and effectiveness of pre-treatment interventions such as ovarian transposition in preserving the ovarian function post pelvic irradiation. Expansion of this review on participants with identical criteria can be performed, to permit further understanding of the post-irradiation gonadal effects.

Keywords: Gonadal effect, Post-irradiation, Time-of-recovery, Intervention, Radiotherapy

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INTRODUCTION

In medical field, various evidence demonstrated the importance of radiotherapy for cancer treatment since the discovery of radiation (1,2). Currently, radiotherapy can be delivered as the primary or part of combination therapy for most cancer therapy regimens (3). Despite the advantage of radiotherapy as part of cancer treatment, the benefit is restricted by the normal tissue tolerance towards radiation injuries (4). The adverse effects induced by radiotherapy restrict its role in the multi-disciplinary therapy of cancer. Following radiotherapy, normal tissue reaction post-radiation treatment differs between patients (5).

Cervical cancer, prostate, cervical and ovarian cancer are among the most common reproductive cancers which occur in the reproductive organs. Ovarian cancer ranks fifth in cancer deaths among women and 85% of people diagnosed with ovarian cancer are diagnosed in the later stages of disease when treatment options are often limited. The survival rate of cancer patients improved through early detection and refined treatment

planning which may include surgery, chemotherapy, radiotherapy and hormonal treatment. However, the patients' quality of life may be affected by the concurrent treatments (6). As the treatment modalities improved, methods to minimize the side effects related to the treatment should also be established. The significant long-term consequences of chemoradiotherapy often include impairment and gonadal dysfunction especially for the treatment to the pelvic area (7). Following radiotherapy, sexual dysfunction is often reported, especially in patients with low-lying rectal tumors (8).

Fertility in women after cancer treatment such as chemotherapy and radiotherapy, is also of particular importance. Previous studies reported ovarian failure in 97% of women post total abdominal irradiation during childhood, and 72% of patients treated pre-puberty (9). Chemotherapy and radiotherapy can be gonadotoxic as they affect the function of ovaries, uterus and hypothalamic-pituitary-gonadal axis. Total body, abdominal or pelvic irradiations can affect the uterus by reducing the uterine volume and spontaneous miscarriage, aside from ovarian damage (7).

There is also an urgent need to examine the gonadal effects on patients underwent pelvic irradiation, and the intervention strategies in reducing these effects. Thus, this scoping review aimed to answer the following

questions: (i) what are the gonadal effects of post-pelvic irradiation among cancer patients; (ii) how long does it take for patients to recover post-pelvic irradiation; and, (iii) what are the approaches in managing these side effects. This review aimed to summarize the existing knowledge from current research, on the effects of radiotherapy on cancer patients and the interventions (pre- and post-treatment) taken to overcome and manage these side effects.

It is important to ensure that the review involved evidence-based knowledge regarding the interventions and strategies in managing the common side effect of pelvic irradiation, which includes urinary problem, diarrhea, fatigue and impotence. Through scoping review methodologies, the adverse effects and opportunities to improve the patients' survival will be discussed explicitly.

MATERIALS AND METHODS

A scoping review of the literature was carried out to provide a narrative synthesis of the side effects of radiotherapy for cancer in daily practices. The phases of this scoping review include: (1) identification of applicable research question(s); (2) identification of relevant studies related to pelvic irradiation; (3) selection of studies with regards to pelvic irradiation; (4) extraction of data for further analysis; and (5) collating, summarizing and reporting the outcomes based on the Arksey and O'Malley (2005) guideline.

Identifying relevant studies

A comprehensive search strategy using Google Scholar, PubMed and Cochrane Library databases was carried out on related terms including "gonadal effect", "gonadal", "radiotherapy", "radiation therapy", "pelvic irradiation", and "rectum irradiation". The search result was last updated in August 2018. References from the retrieved articles were used for further articles' extraction. Studies related to radiotherapy and radiation toxicity with gonadal and gynecological effects were included. The searching process was restricted to articles published in English between January 2000 and August 2018. The articles were imported into an online research management tool to remove duplications. Figure 1 illustrates the selection of studies shown in PRISMA diagram.

Study selection

A total of 18,755 articles were retrieved from the initial search. The exclusion and inclusion criteria were established to narrow down the number of studies. The criteria of inclusion include any information on gonadal effect post-pelvic irradiation and the intervention done for the side effects. Articles about the pre-treatment intervention methods to reduce the side effects from irradiation were also included. On the other hand, meta-analyses, case study reports, scoping review and

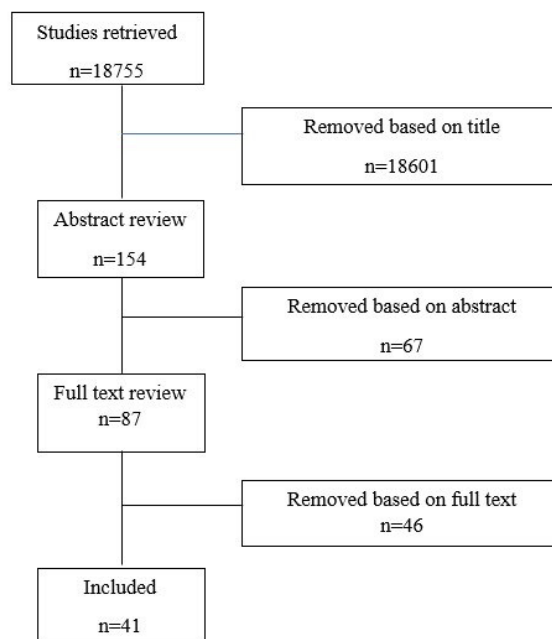


Figure 1: Selection of studies shown in PRISMA diagram. PRISMA diagram visualised the studies selected in this study

systematic review articles were excluded. In the case where different articles reported similar samples, the articles with higher number of samples or those which provide the most comprehensive information were selected. The lists of inclusion and exclusion criteria are shown in Table I.

The number of selected articles were reduced to 154 articles following the application of the inclusion criteria. Detailed screening process and search strategy were developed to ensure the reliability of this review.

Table I: Study inclusion and exclusion criteria

Study characteristics	Inclusion criteria	Exclusion criteria
<i>Design</i>	Trial study; randomised controlled study and non-randomised controlled study; cohort study	Comparison study; case study; diagnostic; prognostic study; systematic review and scoping review
<i>Publication</i>	Peer-reviewed journal; published in English;	Dissertation; poster and any conference proceeding
<i>Participants</i>	All ages; any cancer diagnosis; any phase of treatment; underwent radiotherapy only and/or concurrent therapy; photon therapy; Cobalt-60	Non-cancer gonadal effect; I-131 therapy; proton therapy
<i>Outcome measures</i>	Any gonadal effect; short and/or long-term side effect; pre-treatment and/or post-treatment intervention	Effect from chemotherapy regimens only; non-gonadal effect; phantom study

Following the selection process, Microsoft Excel spreadsheet was used to input the data from the full text articles.

Data extraction

The following data such as article type, publication year, statement of country of origin, study design, sample size and participants were extracted from each selected article. Any disagreements were resolved via discussions among the authors. Animal studies were not accepted. For country of origin, the information includes countries to which the cohort of patients had treatment from, origin of data banks and from the statement of ethnicity. The details of radiotherapy-specific clinical data extracted from the selected articles were listed which includes type of cancer (cancer around pelvic area), dose prescribed, radiotherapy intent (prophylaxis, radical, palliative), type of radiotherapy treatment (conventional, 3D-CRT), side effect, time of recovery and intervention.

Assembling and summarizing the data

The collected data were tabulated and descriptively analyzed. Microsoft Excel was used to assemble the data according to preset variables. All the selected articles were collected to answer these main questions:

1. What are the gonadal effects of pelvic irradiation among cancer patients?
2. What is the time of recovery post-pelvic irradiation?
3. What are the approaches and interventions in managing the side effects?

RESULTS

A total of 18,755 articles were identified in the first round of screening. Among these articles, 87 full-text articles were retrieved in the second round of screening. From this number, only 41 independent articles that fulfilled the inclusion and exclusion criteria were presented. All studies were observational. In brief, 18 out of the 41

(43.9 %) studies were prospective, while the remaining were retrospective. Twenty out of the 41 (48.8 %) studies were carried out in Europe (mostly in Germany), 11 in the North America, 8 in Asia, one in Africa and one in the Oceania.

The distribution of cancer cases and number of participants were summarized based on the diagnosis-tumor stream; GI colorectal cancer, gynecological cancer, bladder cancer, testicular cancer, prostate cancer, hematological cancer, neurological cancer, childhood cancer and heterogenous cancer. Most of the treatment for these cases were radical, however, for GI colorectal cancer, the treatments were divided into radical, adjuvant and neo-adjuvant. Majority of the patients (n=9611) had childhood cancer including Hodgkin's lymphoma, followed by prostate cancer with a total of 1704 participants in 4 trials. Only 3 out of the 41 trials (7.32 %) had mixed cancer populations. Another 22 trials involve cervical, rectal, bladder, testicular, neurological and hematological cancers. For these trials, the average sample size was 310, ranging from 1 to 3390 participants, with fewer than 50 participants in 19 (46.3 %) trials. However, 6 trials had more than 400 participants compared to others.

The presence of gonadal effects is the baseline inclusion criterion for this study. Gonadal effects for males and females are shown in Table II. Thirteen out of 20 studies (65.0 %) reported the presence of ovarian failure and dysfunction as the gonadal effects in females. Sexual dysfunction, infertility, pre-mature menopause secondary amenorrhea and reduced parenthood were reported in the remaining 7 studies. For gonadal effect in males, 8 out of 22 studies (36.4 %) reported hypogonadism, decrease sex hormone and serum testosterone change. Four out of 22 studies (18.2 %) reported infertility, while the remaining studies reported impaired sexual

Table II: Categories of gonadal effects in the studies

Category	Included gonadal effects	No of study
<i>Female gonadal effects</i>	Sexual dysfunction	1
	Ovarian failure/premature ovarian failure/ovarian dysfunction/acute ovarian failure	13
	Infertility	2
	Premature menopause	2
	Secondary amenorrhea	1
	Reduced parenthood	1
<i>Male gonadal effects</i>	Infertility	5
	Impaired sexual function	2
	Temporary azoospermia	1
	Hypogonadism/decrease sex hormone/temporary testosterone decrease/serum testosterone change	8
	Damage to testis	1
	Testicular dysfunction	1
	Gonadal damage/dysfunction	4

function, temporary azoospermia, testicular dysfunction and gonadal damage as the gonadal effects in males.

Interventions introduced in the studies were categorized into pre-treatment, during treatment and post-treatment. The included interventions were defined in Table III. Timing of interventions such as pre, during and post-treatment, varies from immediate to more than several years following the radiation treatment. Variation in the interventions often involved the content, intent, intensity and the duration of the interventions. There were adequate definitions of outcome in 25 out of the 41 studies (61.0 %), i.e. either the interventions were conducted or not. For pre-treatment interventions, 11 out of 13 studies (84.6 %) introduced ovarian transposition, while the remaining involved sperm cryo-conservation and prior radical prostatectomy. For interventions performed during the treatment, 6 out of 9 studies (66.67 %) introduced gonad shielding. Post-treatment interventions which were performed in 4 studies include testosterone replacement therapy, oral contraception and assisted reproduction technique (ART) to improve probability of parenthood. Sixteen out of 41 studies (39.0 %) did not mention any interventions or approaches to overcome the gonadal effects of cancer treatment. Out of 41 studies, only one study had mentioned about the time of recovery post-treatment (10), i.e. temporary testosterone decrease will recover 18 months after the treatment.

Table III: Categories of interventions implemented in the studies

Category	Included intervention	No of study
<i>Pre-treatment</i>	Ovarian transposition/laparoscopic ovarian transposition	11
	Sperm cryo-conservation	1
<i>During treatment</i>	Gonad shield/Testicular shielding	6
	Change method of irradiation	2
	Double-hole belly board	1
<i>Post-treatment</i>	Testosterone replacement therapy	2
	Oral contraceptive	1
	Assisted reproduction therapy (ART)	1
<i>Not stated</i>		16

DISCUSSION

There is an emerging evidence that different forms of radiation treatment for ovarian, testicular, prostate, cervical and bladder cancers give an impact towards a patient's sexual function (11). Reproductive implications of radiotherapy are often raised as potential concerns as most patients were diagnosed at the peak reproductive years. In young cancer survivors, effect on fertility, pregnancy and neonatal outcomes post irradiation are of great concern. In women with pelvic irradiation, the risk of pregnancy-related complications, including spontaneous miscarriages, preterm labour and delivery,

low birthweight and placental abnormalities are higher (12). Close obstetric observation is required as these findings have been attributed to reduce uterine volume, impaired uterine distensibility, damaged uterine vasculature, and endometrial injury.

There is existing evidence that showed the improvement of sexual function in patients with gynecological cancers post-treatment by medication and mechanical devices. Erectile dysfunction was reported to be one of the severe problems in the newly diagnosed patients (13). Previous study showed that patients with decreased sexual function often associated with anxiety and depression compared to patients with unaffected sexual function (14).

Men treated with radiotherapy may develop testicular dysfunction compared to men treated with surgery alone due to decrease serum testosterone levels. Decreased in testosterone levels after radiotherapy may cause anxiety which is a part of psychological problem besides impaired sexual function for both men and women (15). Acute decrease in levels of hormones such as estrogen, progesterone and testosterone in women will lead to irreversible menopause, and the changes in this endocrine axis causes an emergence of menopausal symptoms such as vulvovaginal and clitoral atrophic changes coupled with vaginal thinning, decreased elasticity with resulting dryness and onset of dyspareunia (16).

Hypogonadism is closely related to the side effect of pelvic irradiation, with symptoms of low level of serum testosterone (17). Patients with pelvic malignancy should be well-informed on the risk of temporary or permanent infertility due to testosterone deficiency post-treatment (15).

Ovarian failure is a common adverse effect of pelvic irradiation, to which it affected the pubertal development of patients. Another symptom of ovarian failure is premature menopause before the age of forty. Intervention to reduce the side effect includes ovarian transposition, which is a surgical procedure that change the ovarian position to allow radiation to be directed to cancerous cell only. In order to preserve the ovarian function, patients with cervical cancers, Hodgkin's lymphoma, pediatric sarcomas and rectal cancers are considered for ovarian transposition (3,4,18–27). Previous studies proved the effectiveness of ovarian transposition in preserving the ovarian function for patients with pelvic irradiation, with reduced morbidity (28). Ovarian transposition is also a simple and reliable procedure as it can be done with laparoscopic technique with the aid of camera.

Incomplete or lack of reporting regarding the interventions performed either before, during or after the radiation treatment may affect further clinical research

in determining the accurate course of action in the management of gonadal effects. Detailed reporting is crucial to improve the existing protocol, thus reducing the mortality and morbidity for each case. As technology advances, the complexity arises from the wide range of treated condition, thus, a robust and detailed information for each case are crucial.

Various factors were taken into consideration in order to establish association between gonadal function after the radiation treatment and the intervention performed. According to a previous study, age, radiation dose and BMI did not greatly influence the normal ovarian function after ovarian lateral transposition and radiation treatment, instead, the placement of clip for lateral transposition significantly affect the ovarian function (21). However, another research reported that the consideration of patients' age significantly influenced the result of ovarian transposition (p-value <0.05) (29). The study also showed a correlation between the radiation dose toward the recovery after ovarian transposition, with a p-value of <0.01 (29).

The challenge faced by these studies often involved the completeness of reporting, based on the CONSORT checklist and guidelines by the Radiogenomic Consortium, to allow transparent clinical trial (3,30). Details in the reporting that leads to the outcome of each study are vital, especially in the identification of participants, as each individual is unique and might come from different racial background. Among the criteria listed in the guidelines includes the reporting of ancestry for each patient, which often excluded from the variables. Influence of race and ancestry towards the effectiveness of post-treatment intervention are still unclear, due to limited data and the lack of detailed reporting.

The detail of ethnicities was collected based on the country of origin of each study, where most of the patients recruited reside in close proximity from the hospital. Different races may react differently towards radiation treatment, thus different interventions are necessary after careful research. Radiosensitivity has been shown to be related to the ethnic origin in some studies, e.g. African-American patients were more prone to erectile dysfunction due to their genetic design (3). Most studies were conducted in the Europe, with a total number of 3957 patients involved, which translates to 5.328 patients/million. Since most studies were performed in Europe, most individuals were assumed to be from European ancestry, i.e. Caucasian. The distribution of patients/million population in this study includes Africa with 0.015, Asia with 0.0093, Europe with 5.328, North America with 20.948, South America with 0, and Oceania with 16.104.

Previous studies had proved that allelic frequencies vary between ancestry groups, thus, association between

genetic information and the outcomes post-radiotherapy (with intervention) should be properly represented. However, there is a lack of statement of ethnicities in the studies involved, except for two studies (31,32). Due to the paucity of ancestry statement, the gap of post-treatment outcomes may increase.

This scoping review is limited as many studies only focused on the more common adverse effect of radiation treatments and widely used interventions. Other than that, this review was also limited to studies that were publicly available, i.e. PubMed, Google Scholar and Cochrane Library, within a specific range of years. Thus, cases that are exclusively reported in private and inaccessible databases for example the hospital registries, are not included. This scoping review did not include quality of life as a search term, in order to narrow the review to only gonadal effects and interventions. Incompleteness of data also became the limitation in this study, as some interventions were only mentioned in the discussion. Finally, from this review, it is recommended that gonadal effects of radiation treatment for cancer patients to be included in the reporting, so that suitable intervention can be incorporated before, during or after the treatment.

CONCLUSION

More evidence exists to indicate the potential and effectiveness of pre-treatment interventions for certain cancer types such as ovarian cancer. Ovarian transposition for young female patient with pelvic irradiation can be considered to preserve the ovarian function with reduced morbidity. Improved and detailed reporting on the gonadal effects and interventions on cancer patients who have undergone radiation treatment are crucial, to permit more accurate and detailed review. Paucity of information on the time of recovery post-treatment has been identified which can be used as a key area of focus for future research. It is best to integrate these tools in clinical practice, as it needs considerable attention especially for the benefit of the patients. Expansion of this review on participants with identical criteria can be performed, to permit further understanding of the post-irradiation gonadal effects.

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