Ovarian Function Following Pelvic Irradiation in Prepubertal and Pubertal Girls and Young Adult Women

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Purpose: To analyze the effect of pelvic radiotherapy on ovarian function in prepubertal and pubertal girls and young adult women.
Patients and Methods: In a retrospective monoinstitutional analysis, patients < 30 years of age at diagnosis were included who had been irradiated between 1979 and 1998. The main tumor types were Hodgkin's disease (38%), Ewing's sarcoma (20%) and nephroblastoma (11%). Patients were classified into three groups according to the position of the ovary in relation to the radiation portals. Group 1 was defined by direct irradiation of both ovaries. Group 2 patients were included with both ovaries potentially located in the radiation portals. In group 3, at least one ovary was not directly irradiated. The median follow-up was 128 months.
Results: 16 of 55 analyzed patients were categorized in group 1. In ten of these patients, hormone status was evaluable. The ovarian doses were ≥ 15 Gy. Except for one patient treated with 15 Gy all developed hormone failure. Eight of 14 patients of group 2 were evaluable. Seven of these patients developed ovarian failure. 19 of 24 patients in group 3 were evaluable. Nine of these patients developed ovarian failure. The observed difference in the rate of ovarian failure between the groups is statistically significant ($p = 0.045$).
Conclusion: All patients receiving > 15 Gy to the ovaries developed hormone failure. In one case of a patient receiving an ovarian dose of 15 Gy, hormone failure was not found. In case of pelvic irradiation excluding at least one ovary, approximately half of the patients developed ovarian dysfunction, probably also due to the effects of polychemotherapy.

Key Words: Ovarian function · Pelvic irradiation

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Ovarialfunktion nach Beckenbestrahlung bei Mädchen und jungen Frauen

Ziel: Analyse des Einflusses einer Beckenbestrahlung auf die Ovarialfunktion bei Mädchen und jungen Frauen.
Patienten und Methodik: In einer retrospektiven monoinstitutionalen Analyse wurden Patientinnen evaluiert, die in den Jahren 1979–1998 in der Klinik für Strahlentherapie des Universitätsklinikums Münster bestrahlt worden waren und bei Therapie < 30 Jahre waren. Die häufigsten Tumorentitäten waren Morbus Hodgkin (38%), Ewing-Sarkome (20%) and Nephroblastome (11%). Die Patientinnen wurden in drei Gruppen eingeteilt. Bei Patientinnen der Gruppe 1 wurden beide Ovarien bestrahlt. Bei Patientinnen der Gruppe 2 wurden beide Ovarien potentiell bestrahlt, und in Gruppe 3 wurde mindestens ein Ovar nicht bestrahlt. Die mediane Nachbeobachtungszeit beträgt 128 Monate.
Ergebnisse: Von den analysierten Patientinnen wurden 16 in Gruppe 1 klassifiziert. Bei zehn dieser Patientinnen war der Hormonstatus evaluierbar. Die Ovarialdosis lag bei ≥ 15 Gy. Bis auf eine Patientin, die mit 15 Gy bestrahlt wurde, entwickelten alle weiteren Patientinnen eine Ovarialinsuffizienz. Von 14 Patientinnen der Gruppe 2 waren acht evaluierbar. Sieben davon wiesen eine Ovarialinsuffizienz auf. 19 von 24 Patientinnen in Gruppe 3 waren evaluierbar. Neun davon entwickelten eine Ovarialinsuffizienz. Der Unterschied zwischen den drei Gruppen in Bezug auf das Auftreten einer Insuffizienz ist signifikant ($p = 0{,}045$).
Schlussfolgerung: Alle Patientinnen, die mit > 15 Gy an den Ovarien belastet wurden, entwickelten eine Hormoninsuffizienz. Eine Patientin mit 15 Gy Ovarialbelastung wies keine Ovarialinsuffizienz auf. Wenn mindestens ein Ovar nicht bestrahlt wurde, lag die Insuffizienzrate bei etwa 50%, wahrscheinlich mitbedingt durch die Chemotherapie.

Schlüsselwörter: Ovarialfunktion · Beckenbestrahlung

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Introduction

Radiotherapy is an essential modality in the treatment of pediatric and adult malignancies [14, 24, 26, 28]. Of particular concern in radiotherapy of girls and young women is the effect of pelvic or abdominal radiotherapy on the female reproductive tract. Direct or indirect irradiation of the ovaries can results in hormonal and reproductive dysfunction and, thus, sterility [9, 18, 27]. In patients treated before puberty, irradiation of the ovaries can cause primary ovarian failure with complete or incomplete pubertal development, so that hormone replacement therapy is indicated. The symptoms of hormone depletion in postpubertal patients are comparable to the clinical picture seen in menopausal women including heat waves, irritability and osteoporosis. Hormone replacement therapy is indicated in these patients. In addition, infertility is to be expected [9, 21]. Radiotherapy to the abdomen and pelvis has frequently been applied to girls and young women with Hodgkin's disease, Ewing's sarcoma and nephroblastoma [11, 13, 24].

Ovariopexy reduces the radiation dose to the ovary received by pelvic irradiation. This surgical procedure takes the ovary out of the high dose area of irradiation and may therefore reduce radiation-associated side effects to the reproductive organs [5, 6, 8, 19]. Apart from radiotherapy, ovarian function can be impaired by ovariopexy itself and also by various chemotherapeutic agents [7, 11, 15, 17, 23, 29].

In a retrospective monoinstitutional analysis we have evaluated the effect of pelvic irradiation on ovarian function in prepubertal and pubertal girls and young adult women with different malignancies needing pelvic irradiation as part of their treatment protocol.

Patients and Methods

Study Design

In a retrospective analysis, ovarian function was evaluated in female patients who had received radiotherapy to the pelvis at the Radiotherapy Department of the University Hospital in Muenster, Germany, between January 1979 and December 1998 and were between 1 and 30 years of age at the time of irradiation. Patients were included in the analysis when a minimum follow-up of 2 years after irradiation was possible. A standardized questionnaire was used to document the extent of the disease, the surgical procedures, chemo- and radiotherapy.

Pubertal development, ovarian function and the need for hormone replacement therapy were documented at the time of treatment and during follow-up. The clinical and hormonal data of the clinical follow-up were retrieved from the charts of the Department of Radiotherapy and the Department of Pediatric Hematology and Oncology. For missing and/or additional data the general practitioner, the gynecologist and occasionally the patient were contacted.

Radiotherapy

The documentation of radiotherapy included the evaluation of the radiotherapy plan, the simulator films, the radiation dose, and the fractionation. In some patients, the ovaries had been clipped during a previous surgical procedure prior to radiotherapy. In these cases, the position of the ovaries in relation to the radiation field was visible on the simulation films. In all other patients, it was assumed that an ovary was in the radiation field when irradiation was given to the whole ipsilateral hemipelvis. The ovary was considered potentially included in the radiation field when parts of the ipsilateral pelvis were shielded. When the radiation field had spared one hemipelvis, this ovary was regarded as not being included in the radiation field.

Patients were classified into three groups:

- group 1 included patients with irradiation of both ovaries or patients with unilateral ovariectomy and irradiation of the remaining ovary;
- group 2 included patients in whom the ovarian function was possibly affected by radiotherapy, e.g., patients with potential direct irradiation to both ovaries, definite irradiation to one and potential irradiation to the other ovary or patients who following unilateral ovariectomy had potential irradiation to the remaining ovary;
- group 3 included patients in whom one or both ovaries were definitely not included in the radiation field.

Toxicity

Ovarian function was documented by serum levels of lactate dehydrogenase (LH), follicle-stimulating hormone (FSH), estradiol, progesterone, and prolactin. FSH levels > 25.8 U/l with estradiol levels between 10.00 und 39.52 pg/ml were regarded as hypergonadotropic hypogonadism. Clinical parameters included delayed pubertal development, age at menarche, irregularities of the menstrual cycle, secondary amenorrhea, and clinical symptoms of hormone deficiency. It was also documented when hormone replacement therapy was taken.

Statistics

The data of the documentation forms were analyzed in SPSS. χ^2-test was used for statistical analysis.

Results

55 patients were included in this analysis. The median age at the time of radiotherapy was 15 years (range: 1–30 years). The diagnoses of all patients are summarized in Table 1. Hodgkin's disease (38.2%), Ewing's sarcoma (20%) and nephroblastoma (10.9%) were the three most frequent diagnoses. 48 patients (87.3%) received chemotherapy in addition to radiotherapy. Seven patients had a bilateral, three patients a unilateral ovariopexy. Three patients had a unilateral ovariectomy before radiotherapy.

16 patients were in group 1, 14 patients in group 2, and 24 patients in group 3. Due to missing simulator and verification films, group assignment was not possible in one patient. The median follow-up for patients with evaluable hormone status was 128 months.

Table 1. Distribution of tumor histologies.

Tabelle 1. Verteilung der Tumorentitäten.

Diagnosis	Patients (n)
Hodgkin's disease	21
Ewing's sarcoma	11
Nephroblastoma	6
Rhabdomyosarcoma	4
Osteosarcoma	2
Neuroblastoma	2
T cell lymphoma	1
Teratoma	1
Adenocarcinoma (Gartner's duct)	1
Synovial sarcoma	1
Pheochromocytoma	1
Dysgerminoma	1
Keloid	1
Heterotopic ossification	1
Unspecified sarcoma	1
Total	55

Group 1

Hormonal evaluation was possible in ten of 16 patients. No data were available in six patients. Two of them were still prepubertal at the time of evaluation; one had Turner's syndrome with gonadal dysgenesis, and it could not be distinguished whether hormonal levels were unnormal due to the treatment or due to the syndrome. In three patients, neither the records nor the local physicians could give any information about the hormone status. Furthermore, it was not possible to contact the patients directly either because they have moved abroad or had died of disease.

Nine of the ten evaluable patients developed ovarian insufficiency, all received hormone replacement therapy. Ovarian insufficiency was confirmed in seven patients by postmenopausal gonadotropin levels together with low estradiol levels, one patient had secondary amenorrhea following therapy, and one patient had postmenopausal symptoms when hormone replacement therapy was omitted. The radiation dose to the ovaries ranged from 15 to 60 Gy (see Table 2). Seven out of nine patients received chemotherapy.

Table 2. Doses to the ovaries and ovarian insufficiency of patients in group 1.

Tabelle 2. Ovarialdosen und Ovarialinsuffizienz bei Patienten in Gruppe 1.

Dose to the ovaries in each patient (Gy)	Ovarian failure
15.00	No
15.00	Yes
18.00	Yes
25.00	Yes
25.00	Yes
29.40	Yes
30.00	Yes
32.00	Yes
50.00	Yes
60.00	Yes

One patient with a diagnosis of Hodgkin's disease received polychemotherapy and radiotherapy to both ovaries at the chronological age of 17 years, but did not develop hormonal insufficiency. The radiation dose to the entire pelvis was 15 Gy with fractions of 1.5 Gy/day. Another patient also treated with polychemotherapy and 15 Gy irradiation to both ovaries showed ovarian insufficiency. The fractionation was 1.5 Gy/day. Her chronological age was 2 years at the time of treatment.

Group 2

14 patients were in group 2; information about the hormonal status was available in eight patients, no information could be obtained in six patients.

Ovarian insufficiency was documented in seven of the eight evaluable patients. Four patients had postmenopausal gonadotropin and low estradiol levels, three patients had secondary amenorrhea. The radiation dose to the pelvis ranged from 38 to 56 Gy. Three patients were on hormone replacement.

One patient had normal ovarian function. All eight patients received polychemotherapy.

Group 3

Ovarian function was evaluable in 19 of 24 patients. Ten patients had normal ovarian function. Nine patients developed ovarian insufficiency, confirmed in seven patients by postmenopausal gonadotropin and low estradiol levels and in two patients by secondary amenorrhea. Two patients received hormone replacement therapy. Eight of the nine patients with ovarian failure and nine of the ten patients with normal ovarian function received polychemotherapy. The diagnoses of patients treated with hormonal failure were Hodgkin's disease (four patients), Ewing's sarcoma (four patients), and T-cell lymphoma (one patient). The diagnoses of patients treated without signs of hormonal failure were Hodgkin's disease (four patients), nephroblastoma (three patients), neuroblastoma (one patient), rhabdomyosarcoma (one patient), and keloid formation (one patient). In the two groups, no difference in the distribution of gonadotoxic cytostatic substances was observed. The median age at chemotherapy was 18.5 years (range: 13–21 years, one patient without chemotherapy) in patients who had ovarian failure. In patients without hormone failure in group 3, the median age at chemotherapy was 6 years (range: 9 months to 18 years, one patient without chemotherapy). The median dose of radiotherapy in patients showing ovarian failure was 40 Gy (range: 20–54 Gy) and 24 Gy (range: 12–32 Gy) in the group of patients without signs of ovarian failure.

No data were available in five patients, one of them is still prepubertal.

Ovariopexy

Ovariopexy was performed in ten patients. In three patients, both ovaries were included in the radiation field despite ovariopexy. These patients are included in group 1. One patient developed hormonal insufficiency; in two patients, the hormone status was not evaluable.

In seven patients, direct radiotherapy to at least one ovary was avoided by ovariopexy. These patients are included in group 3. Four patients did and three did not develop hormonal failure (Table 3).

Children

Two patients had children following radiotherapy. The treatment of these mothers was categorized in group 3.

Statistical Evaluation

The difference in the occurrence of ovarian failure according to the three groups is shown in Table 4. The difference between the groups is statistically significant ($p = 0.045$).

Discussion

Radiotherapy is an essential modality in the treatment of malignant tumors. Particularly in malignancies of childhood and adolescence, very good cure rates have been obtained within the last 20 years. Therefore, the knowledge of treatment-associated toxicity is very important [4]. In a number of tumors, radiotherapy to pelvic structures is necessary. Pelvic lymph nodes are frequently irradiated in patients with Hodgkin's disease [11]. Furthermore, in patients with Ewing's sarcoma of the pelvis, with nephroblastoma and with rhabdomyosarcoma of the genitourinary tract [13, 24], pelvic irradiation may be necessary. In girls and young women, hormonal failure is a frequent late effect when the ovaries are irradiated [12]. Ovarian failure is observed also when using combination chemotherapy alone. A number of drugs carry a particularly high risk of inducing ovarian failure, i.e., cyclophosphamide, ifosfamide, cisplatinum, vinblastine, busulfan, BCNU, and CCNU [7, 11, 17, 23, 29]. Drug-associated ovarian failure is dose- and age-dependent [25] – older patients having a higher risk of gonadal damage [1, 12]. Following treatment with MVPP, COPP and ChlVPP for Hodgkin's disease, ovarian failure was observed in 38–57% of patients. Normal ovarian function in women > 35 years at the time of treatment with these regimens is rarely maintained [12]. Longitudinal studies have shown that in younger women oligomenorrhea may be followed by a return to a normal menstrual cycle. An early onset of menopause can follow gonadotoxic treatment despite initial regular ovulation [2]. The association between age and ovarian failure is also known for patients receiving pelvic radiotherapy in Hodgkin's disease and other malignancies [11].

Radiation doses < 4 Gy usually do not cause permanent sterility [22]. In patients mostly > 40 years, ovarian doses of 5–10.5 Gy in one to three fractions for hemorrhagic metropathy resulted in ovarian failure in 97% [3]. In young patients, an estimated dose of 20 Gy is thought to be required to produce consistently permanent ovarian failure [16]. It is suspected that the combination of pelvic irradiation and chemotherapy will increase the risk of ovarian damage. There is no indication so far that the offspring of patients who received cancer treatment before conception are at a conceivably higher risk of teratogenic effects or of developing malignancies [10].

In our retrospective analysis, ovarian function was evaluated in girls and young women who received pelvic irradiation. It is very difficult to localize ovaries on CT scan and impossible to see their position on simulator films when no metal clips are used for localization. Therefore, we have estimated the likelihood for each ovary to be included in the radiation field. The ovary was considered irradiated when the ipsilateral hemipelvis was in the irradiation field. When only parts of the ipsilateral hemipelvis were irradiated, the ovary was considered potentially irradiated. Due to the difficulties in exactly locating the ovaries, we did not try to estimate scat-

Table 3. Ovariopexy and ovarian insufficiency.

Tabelle 3. Ovariopexie und Ovarialinsuffizienz.

Site of ovariopexy	Group	Ovarian insufficiency
Bilateral	1	Yes
Bilateral	1	Unknown
Bilateral	1	Unknown
Bilateral	3	Yes
Left ovary	3	Yes
Bilateral	3	Yes
Bilateral	3	Yes
Right ovary	3	No
Bilateral	3	No
Right ovary	3	No

Table 4. Occurrence of ovarian insufficiency in the different groups. Statistical significance of groups 1 versus 2 versus 3: $p = 0.045$.

Tabelle 4. Auftreten von Ovarialinsuffizienzen in Abhängigkeit von der Gruppenzuordnung. Statistische Signifikanz der Gruppen 1 versus 2 versus 3: $p = 0{,}045$.

Group	Ovarian insufficiency			Total
	No	Yes	Not evaluable	
1	1	9	6	16
2	1	7	6	14
3	10	9	5	24
Total	12	25	17	54

ter doses to the ovary. Patients were classified into three groups. In group 1, the whole ovarian tissue was included in the radiation field. In group 2, both ovaries were at least potentially in the radiation field. In group 3, at least one ovary was not irradiated.

Ovarian failure was diagnosed when estradiol levels were low and gonadotropins levels were elevated. In addition, secondary amenorrhea, menopausal symptoms or sex hormone replacement therapy were regarded as indicators of ovarian failure.

There is a statistically significant difference in the incidence of ovarian failure amongst the three groups even when the patients with unknown hormonal status are included in the analysis (Table 4). There were fewer patients with ovarian failure in group 3.

In group 1, in whom both ovaries were irradiated, there were nine ovarian insufficiencies in ten patients. In one patient, normal ovarian function was documented. This 17-year-old patient with diagnosis of Hodgkin's disease treated with polychemotherapy and irradiation received 15 Gy to whole pelvis in daily fractions of 1.5 Gy. The total dose was < 20 Gy, a dose considered to cause ovarian failure in most patients [20, 25]. Two further patients received pelvic irradiation with doses < 20 Gy (Table 2). In both patients, ovarian failure was diagnosed. The second patient treated with 15 Gy pelvic irradiation received daily fractions of 1.5 Gy at the age of 2. The patient who received 18 Gy pelvic irradiation was treated at the age of 20.

In group 2, ovarian failure was observed in seven out of eight evaluable patients. The high incidence of ovarian failure is very likely due to the fact that in this group, the ovaries still received a considerable radiation dose and additional chemotherapy was given.

In group 3, nine out of 19 evaluable patients showed ovarian failure, ten had normal ovarian function. Two differences were of note between these two patient groups. First of all, the median dose of radiotherapy to the pelvis was different. It was 40 Gy (range: 20–54 Gy) in the group of patients that developed hormone deficits and 25 Gy (range: 12–32 Gy) in the patients who did not develop ovarian failure. Furthermore, a difference between the age at the time of treatment and hormone deficiency could be observed. The median age at the onset of chemotherapy was 18.5 years (range: 13–21 years, one patient without chemotherapy) in patients who had ovarian failure and 6 years (range: 9 months to 18 years, one patient without chemotherapy) in patients without hormone failure. No difference in the distribution of gonadotoxic cytostatic substances was observed. Therefore, the observed effects may represent a combined effect of scatter irradiation and polychemotherapy with an increased toxicity in older patients.

Ovariopexy was performed in ten patients. In three patients both ovaries were still in the radiation field. In seven patients, at least one ovary was outside the radiation field. In this group, there were four patients with ovarian failure and three patients with normal ovarian function. The rate of ovarian failure in these patients is comparable to the rate observed in patients of group 3. An increased rate of hormonal failure due to complications of ovariopexy (necrosis, tissue damage) could not be observed. Similar results were obtained in patients with cervical carcinoma. Ovarian transposition resulted in ovarian preservation in nearly all patients treated with surgery alone and in about half of the patients treated with external-beam pelvic radiotherapy [5, 19]. In women receiving ovariopexy before radiotherapy of Hodgkin's disease, lateral oophoropexy was more effective than midline fixation [6].

Conclusion

Radiation to the pelvis in childhood and adolescence is associated with a considerable risk of ovarian failure, particularly when one or both ovaries are included in the radiation field. All patients who received radiation doses to the ovaries > 15 Gy showed signs of ovarian failure. Also, patients who only had scatter dose to at least one ovary showed signs of ovarian failure in a considerable proportion due to the additional effects of chemotherapy. Oophoropexy is a useful technique to avoid high doses to the ovaries.

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