**Long-term effects on gonadal function after treatment of colorectal cancer: A systematic review and meta-analysis**

Running title: Gonadotoxictity and risk of infertility of colorectal cancer

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**ABSTRACT**

**Background:**

The incidence of colorectal cancer (CRC) is increasing in the population under 50 years of age, with more than 10% of cases occurring in young adults. Fertility preservation counselling has therefore received increased attention in this younger patient population. Treatment of CRC is often based on multimodal therapies, including surgery, radiotherapy, chemotherapy and, more recently, immunotherapy, which makes it difficult to estimate the expected effect of treatment on fertility. We therefore systematically analysed the published literature on the gonadotoxic effects of CRC treatments in order to better advise patients on the risk of infertility and the need for fertility preservation measures. This systematic review and meta-analysis is part of the FertiTOX project (www.fertitox.com), which aims to reduce the data gap regarding the gonadotoxicity of oncological therapies.

**Objectives:**

To evaluate the potential impact of CRC therapies on gonadal function to allow more accurate counselling regarding infertility risk and the need for fertility preservation measures prior to oncological therapy.

**Materials and methods:**

A systematic literature search was conducted in Medline, Embase and Cochrane CENTRAL up to March 2024. A total of 22 out of 3592 studies were included in the review. Outcomes were defined as clinically relevant gonadotoxicity, indicated by elevated follicle-stimulating hormone (FSH) and/or low anti-Müllerian hormone (AMH) levels and/or need for hormone replacement therapy in women and azoo/oligozoospermia and/or low inhibin B levels in men. Studies with < 9 patients were excluded from the meta-analysis.

**Results:**

The qualitative analysis included 22 studies with 1570 subjects (723 women, 847 men). The quantitative synthesis showed an overall prevalence of clinically relevant gonadotoxicity of 23% (95% CI: 13 - 37%). In women the prevalence was 27% (95% CI: 11-54%) and in men 18% (95% CI: 13-26%). Subanalysis by type of CRC was only possible for rectal cancer, where the prevalence was 39% (95% CI: 20-64%). The prevalence of clinically relevant gonadotoxicity was only 4% (95% CI: 2-10%) in patients receiving chemotherapy alone, 23% (95% CI: 10-44%) in those receiving radiotherapy alone, and as high as 68% (95% CI: 40-87%) in those receiving radiochemotherapy.

**Conclusion:**

This first meta-analysis of clinically relevant gonadotoxicity of CRC therapies provides a basis for counselling on the risk of infertility and the need for fertility preservation measures. Despite the low prevalence of gonadotoxicity in cases receiving chemotherapy alone, fertility preservation is still recommended due to the uncertainty of subsequent therapy and the lack of large longitudinal data on individual treatment effects. Further prospective studies are needed to investigate the individual impact of CRC treatment on gonadal function and to estimate the effect of new treatment modalities such as immunotherapies.

**Key words:** Colorectal cancer, infertility, oncological treatment, FertiTOX, FertiPROTEKT

**Introduction**

Colorectal cancer is one of the most frequently diagnosed cancer with about 10% of all new diagnosed cases of cancer [1]. In studies colon and rectal cancer are mainly described together as colorectal cancer. The most prevalent histological subtype is the adenocarcinoma. The UICC 2003 (Union for International Cancer Control) defines rectal cancer by the distance from the anocutaneous line smaller than 16cm [2]. The bowl cancers that occur more cranial are considered to be colon cancer. In contrast in the USA, colon carcinomas are defined by a distance of 12cm from the anocutaneous line, justified because of the higher rate of local recurrence of tumors below 12cm [3].

The incidence of colorectal cancer (CRC) is increasing in the population under 50years of age, with more than 10% of cases occurring in young adults [4] . The groups of familiar predisposition of colon cancer (without genetic correlation), hereditary colorectal cancer (like hereditary non-polyposis colorectal cancer or adenomatosis polyposis syndrome) or chronic inflammatory bowel disease are accompanied with younger age of onset [5–8].

Treatment of CRC is often based on multimodal therapies, including surgery, chemotherapy, radiotherapy and, more recently, immunotherapy, which makes it difficult to estimate the expected effect of oncological treatment on fertility. Advances in medical therapy have led to improve 5-year survival for CRC of approximately 65% for all tumor stages. For the early stage I the 5-year survival is about 90% [9,10].

There is increased awareness and knowledge regarding the toxicity of cancer treatments and long-term complications such as hormonal changes, uterine changes or loss of ovarian function due to chemotherapy and radiotherapy leading to infertility in the group of long-term survivals [11]. The standard chemotherapy regime, indicated from stage II/III on, is called FOLFOX and includes folinic acid, 5-fluoruracil, capecitabine or oxaliplatin. The chemotherapy is often completed by a radiotherapy especially in rectal cancer [12].The toxicity of the chemotherapy is estimated to be low to moderate, but the radiotherapy of the pelvis is supposed to harm the gonads and uterus. This effect could be reduced by fertility preservation or transposition of the organs [12,13].

Therefore, fertility preservation has become more important and medical guidelines and clinical practice take fertility preservation increasingly into account. The handbook of the network FertiPROTEKT and the ESHRE guideline Fertility preservation are one of the few sources which contains specific recommendations for fertility preservation in colorectal cancer. Data on the gonadotoxicity of the multimodal treatment of CRC is still limited and therefore the recommendations are still rare.

Counselling about fertility preservation is crucial before the start of a potential gonadotoxic therapy. We therefore systematically analyzed the published literature on the gonadotoxic effects of CRC treatments in order to better advice patients on the risk of infertility and the need for fertility preservation measures. This meta-analysis is part of the FertiTOX [14] project ([www.fertitox.com](http://www.fertitox.com)), organized by FertiPROTEKT ([www.fertiprotekt.com](http://www.fertiprotekt.com)), which aims to fill the data gap on gonadotoxicity of cancer therapies to enable more accurate counseling regarding fertility preservation [15,16].

The treatment of colorectal cancer is heterogenous depending on the location, stage and weather it is a colon or a rectal cancer, which makes it difficult to summarize these therapies. The intention of this systematic review and meta-analysis is to provide better guidance for oncologists and reproductive physicians regarding the estimated risk of infertility, when they counsel patients about fertility preservation.

# **Materials and methods**

Registration of protocols

This study protocol has been registered in the Prospective International Registry of Systematic Reviews (PROSPERO; Registry Number: CRD42024511944).The Preferred Reporting Criteria for Systematic Reviews and Meta-Analyses (PRISMA) were used [17] .

### **Search strategy**

We conducted a systematic literature search of Medline, Embase, and Cochrane CENTRAL databases in March 2024 (Figure 1). A medical information specialist developed an initial MEDLINE search strategy and tested a basic reference list. Following refinement and query, complex search strategies were developed for each information source based on database controlled vocabularies (thesaurus terms/headings) and text terms.

Synonyms, acronyms, and similar terms were included in the text word search. We limited our search to publications from 2000 to the present. Our search terms included all types of colorectal cancer.

A double-negative search strategy based on the Ovid "humans-only" filter was used to exclude animal-only studies from the MEDLINE and Embase searches. Detailed final search strategies are provided in the supplementary file (S1). In addition to the electronic database search, reference lists and bibliographies of relevant publications were reviewed for relevant studies. All identified citations were imported into the software Covidence, a tool for systematic reviews. Duplicate records were removed [18] .

### **Inclusion and exclusion criteria**

Studies were independently assessed for inclusion using Covidence software ([www.covidence.org](http://www.covidence.org)) [19] by four investigators (CA, AV, HH, and EP). All original articles that provided information on colorectal cancer type, therapy, and fertility outcomes with numbers sufficient to calculate prevalence were included. Definitions of clinically relevant gonadal toxicity are described in Table 1. Studies that did not have an assessment of gonadal toxicity in accordance with the definitions in Table 1 were excluded.

### **Data extraction**

The extracted data were abstracted and independently reviewed by four investigators (CA, AV, HH, and EP). Characteristics of the study populations (patient age at diagnosis and outcome, duration of follow-up, type of CRC, type of oncological treatment, and fertility parameters) were the principal variables of interest. Discrepancies were discussed and resolved by consensus.

**Quality assessment**

### The Newcastle-Ottawa Scale (NOS) 17 was used to assess the quality of individual studies. The scoring of individual studies was based on three parameters: subject selection (0-4 stars), comparability (0-2 stars), and study outcome (0-3 stars). The scoring was as follows: good quality (= 3 or 4 stars in selection AND 1 or 2 stars in comparability AND 2 or 3 stars in outcome/exposure), fair quality (= 2 stars in selection AND 1 or 2 stars in comparability AND 2 or 3 stars in outcome/exposure), and poor quality (= 0 or 1 star in selection OR 0 stars in comparability OR 0 or 1 stars in outcome/exposure). All included studies were reviewed by CA, AV, HH, and EP to independently assess the risk of bias; disagreements were resolved by consensus. Scoring was conducted according to the terms listed in Table 4.

### **Data synthesis**

The prevalence of infertility in men and women with colorectal cancer after oncological therapy was the primary outcome of our systematic review. Subgroups with chemotherapy alone, radiotherapy alone, and the combination of both types of treatment were performed. To calculate the prevalence, the number of patients who met the criteria for infertility was divided by the number of patients at risk of infertility as reported in the individual studies. For the pooled prevalence, statistical analyses were performed using the "metafor" function of the R software (R Core Team, Vienna, Austria, 2013). Heterogeneity was assessed using Cohen's Q statistic and I statistic2. In the presence of high heterogeneity, random effects models were used. Studies with unspecified treatment were excluded for outcome assessment to provide clinically meaningful estimates in the meta-analysis.

# **Results**

# **Results of the systematic review**

A total of 67 out of 3592 studies were included in full-text analysis after screening of 3581 abstracts (11 studies were presented double by Convidence). The main reason for excluding the 3525 abstracts were lack of clear reference to fertility or no original work. Finally, 22 articles were included in the systematic review and meta-analysis. (Fig.1). 45 studies were excluded because they did not meet the prespecified inclusion criteria.

### **Study characteristics**

The characteristics of the 22 studies are summarized in Table 2 and 3.

The included studies were retrospective (n=10) and prospective (n=12). The reviewed studies reported menstrual status, gonadal dysfunction and hormonal changes as female fertility outcomes. Male fertility parameters includes sperm analysis and hormonal changes after treatment. 10 studies were conducted with men, 11 with women and 1 with both genders.

With the exception of five good-quality articles, the majority (n=17) were rates as being of poor methodological quality. This was mainly due to the lack of a comparison group (Table 4).

Altogether a total of 1634 patients reported a history of “colorectal cancer” (we here added all described cancers: CRC, rectal and colon cancer) and underwent oncological treatment, of which 775 (47,4%) women and 859 (52,6%) men were eligible for fertility analysis. Differentiated by cancer type there are 1041 rectal cancers, of which were 208 (20%) women and 833 (80%) men. 153 colon cancers, of which were 145 (94,8%) women and 18 (11,8%) men. 430 patients were described to have CRC, 422 female (98,1%) and 8 male (1,5%).

Study sample sizes ranged from 4 to 361 patients (4 to 361 in females and 8-290 in males). The studies were conducted in various regions, including Europe (n=8), Asia (n=9), the USA (n=3) and Canada (n=2). Colorectal cancer includes colon and rectal cancer. We found 1 study for ~~1~~ colon cancer, 16 for rectal cancer and 6 for colorectal cancer.

Study participants comprised post-pubertal males and females, with a median age of 34,5 years (range 23-43 years) in females and 57,3 years in male (range 35-71 years) at the time of cancer diagnosis. The age of outcome evaluation was very inhomogeneous, because the Follow up was performed after 6 weeks to 12 years.

The studies generally had follow-up periods, with a median of about 2,4 years and a range of 6 weeks to 12 years.

Treatment options included operation, chemotherapy and radiotherapy. Specific information on the patients was sometimes missing.

### **Prevalence of infertility**

The prevalence of infertility in patients with a history of colorectal cancer ranged overall between 13% and 37%, in females between 11-54%, and between 13%-26% in males. Retrospective studies of long-term survivors with mean follow-up of 4.48 years in women [20] with 75% prevalence of infertility and men [21] with mean follow-up of 5 years and 16% prevalence of infertility.

# **Results of the meta-analysis**

### 12 studies that assessed fertility outcomes were excluded to provide clinically meaningful estimates.

### **Pooled overall prevalence of infertility after all types of treatment**

Ten studies were eligible for inclusion in the analysis of the overall prevalence of infertility. These studies comprised 778 female and 859 male cases. Consequently, patients were categorized according to their gender, and oncological therapy (i.e. different types and doses of chemotherapy and radiotherapy and combinations of different therapies). The prevalence of each of these studies and a summary of the prevalence are shown in Figs. 2,3,4. The overall prevalence was 23% (95% CI: 13-37%) in general, 27% (11-54%) for women and 18% (13-26%) for men. The heterogeneity test revealed significant heterogeneity among the studies I2 = 94%, p < 0.01, I2 = 96%, p < 0.01. and I2 = 60%, p 0.04.

### **Subgroup analysis**: Infertility in patients on the basis of disease type

To evaluate the prevalence of infertility according to the type of colorectal cancer (colon cancer vs. rectosigmoid cancer). The analysis was only possible in the rectosigmoid group. (Figs. 5).

The prevalence of infertility was 39% (95% CI: 0.20–0.64) (Fig. 5). Data heterogeneity was (I2 = 95%, p < 0.01).

### **Subgroup analysis**: Infertility in patients on the basis of therapy type

To evaluate the prevalence of infertility according to the type of colorectal cancer (chemotherapy only, radiotherapy only and the combination of treatments). Three groups of patients were analyzed (Figs. 6,7,8). The prevalence of infertility in chemotherapy only group was 4% (95% CI: 0.2–0.10) (Fig. 6). The prevalence of infertility in radiotherapy only group was 23% (95% CI: 0.10–0.44) (Fig. 7). The prevalence of infertility was found to be highest in the combination of chemotherapy and radiotherapy with 68% (95% CI: 0.40–0.87) (Fig. 8). The heterogeneity test revealed significant heterogeneity among the studies I2 = 91%, p < 0.01, I2 = 89%, p < 0.01. and I2 = 0%, p 0.04, respectively.

# **Discussion**

This systematic review and meta-analysis aimed to analyze the prevalence of gonadotoxicity following colorectal cancer to improve fertility counseling. To the best of our knowledge, this is the first meta-analysis of the overall prevalence of infertility after multimodal oncological treatment of colorectal cancer.

Our review revealed the following critical findings: First, the overall pooled prevalence of gonadal toxicity in the general cancer survivor population who underwent CCR was moderately high, around 23% (95% CI: 13–37%). When categorized by gender, it was observed to be 27% (95% CI: 11–54%) for women and 18% (95% CI: 13–26%) for men. Second, in subgroup analysis, a significantly high tendency was noted for the rectosigmoid group, with an infertility prevalence of 39% (95% CI: 0.20–0.64). Third, the prevalence of gonadal toxicity was significantly tied to the combination of radiotherapy and chemotherapy 68% (95% CI: 0.40–0.87) compared to radiotherapy alone with 23% (95% CI: 0.10–0.44) or chemotherapy alone with 4% (95% CI: 0.2–0.10).

In our review, we identified five retrospective studies of good quality [20–24]. A subgroup analysis for colon cancer was unfeasible due to the predominant use of mixed therapeutic cohorts in the studies. These cohorts included various combinations and doses of chemotherapy and radiotherapy, aggregated results, and mixed-age populations.

The gonadotoxic effects on fertility depend on the patient's age at treatment, the types of drugs used, the cumulative dose of chemotherapy and radiotherapy, the type of surgery, and the patient's reproductive status. It is important to note that treatment tends to be more aggressive, advanced, and systemic in younger patients compared to that of older patients with CRC [25–28].

Regarding the gonadotoxic effects of chemotherapeutic agents specific to colorectal cancer treatment, fluorouracil is less likely to impact fertility compared to cyclophosphamide. It has a relatively low risk of amenorrhea in women and may cause a temporary decrease in men's sperm count. Other agents, like oxaliplatin, can also cause transient gonadal toxicity [29,30]. In women, oxaliplatin treatment may cause transient ovarian toxicity and amenorrhoea. It can also result in a decrease in anti-Mullerian hormone levels and an increase in follicle-stimulating hormone levels. These effects were observed by Levi et al. (2015) among 19 patients (11 women and eight men) who underwent hormone level assessments before and 6 months after oxaliplatin treatment [29]. This concerns particularly ~~to~~ FOLFOX, a combination chemotherapy including folinic acid (leucovorin, calcium folinate, or FA), fluorouracil, and oxaliplatin). Cercek et al. (2013) demonstrated that 16% of women under 50 years experienced persistent amenorrhea after FOLFOX chemotherapy. However, the study was not adequately powered to distinguish the difference in amenorrhea rates between women under 40 and those aged 40–50 [28].

According to the guidelines of the FertiPROTEKT network, our results demonstrate that the chemotherapy-induced risks for colorectal cancer are low to moderate but significant for pelvic radiotherapy [31]. For rectal cancer, high-dose pelvic radiotherapy is a common treatment. In women, it has been observed that doses of less than 2 Gy can cause a 50% reduction in the number of immature oocytes in the ovaries [20,32,33] . In more than 90% of patients with rectal cancer, radiotherapy doses of 45–50 Gy cause premature menopause [34].

However, predicting the impact of radiotherapy on fertility is challenging, particularly for rectal cancer patients who receive high doses of radiation directly to the uterus. This significantly escalates the occurrence of unfavorable pregnancy outcomes and decreases fertility [35,36]. In men diagnosed with rectal cancer, the testicles receive between 3% and 17% of the administered radiation dose. Consequently, radiation exposure to the testicles in men of any age with primary rectal cancer can lead to physical and psychological issues, diminished sexual function, and reduced fertility [37,38].

In recent years, one of the innovative fields of CRC therapy research has been immunotherapy [31]. Neoadjuvant immunotherapy may prove to be effective in patients with microsatellite-stable colorectal cancer undergoing radiation and chemotherapy. The long-term impact of anti-vascular endothelial growth factor monoclonal antibody inhibitors, such as bevacizumab, on patients' fertility remains unclear [39]. The rate of ovarian failure in CRC patients who received bevacizumab in conjunction with FOLFOX was 34%, in contrast to 2% in those who did not receive bevacizumab. Additionally, about 20% of women regain ovarian function following the cessation of bevacizumab treatment, thus indicating a potential reduction in female fertility. However, no studies have investigated its effect on male fertility. In terms of surgery, bladder and sexual functions of patients with rectal cancer may also be affected, primarily due to the division of the pelvic autonomic nerves during the procedure [40].

Previous studies have indicated that low anterior resection (LAR) for rectal cancer can impact patients' sexual functions and fertility [41]. Machačkova et al. evaluated the outcomes of sexual function, discovering that both International Index of Erectile Function (IIEF) and Female sexual Function Index (FSFI) were considerably lower 6 months following the closure of ileostomy [42].

In men, neurological damage could affect ejaculation. Locally advanced disease could necessitate the removal of reproductive organs. Besides neurological damage influencing sexual function, the presence of a stoma is also associated with poorer sexual function and action [43,44]. The findings from Goossens et al. indicate that between 66% and 100% of cancer patients receiving potentially gonadotoxic treatment were interested in understanding the impact of the treatment on their fertility [45].

Additionally, many rectal cancer patients might benefit from fertility preservation treatments, including those who have undergone surgery. Fertility can be affected to different extents by surgery alone, or in combination with chemotherapy and radiotherapy. Surgical resection is the primary treatment for early localized CRC. To comprehend the effects of CRC treatment on gonadal function in patients of reproductive age, it is essential to analyze and evaluate data on hormonal indicators and reproductive health in the young CRC patient population. This understanding will help in providing supporting strategies for these patients on the one hand and improving their fertility and overall quality of life on the other.

Although we strictly followed the recommendations for producing high-quality evidence summaries, there are some limitations to our study: Firstly, the majority of the included studies relied on retrospective data, which did not provide necessary information on the long-term impact on fertility. Secondly, significant heterogeneity among the studies related to differences in treatment and varying characteristics of the study populations prevented the performance of additional subgroup analyses. These would have been highly relevant for pre-treatment fertility preservation counseling. For example, the population of men were mainly above the age of the standard reproductive age men. Finally, a limited and short follow-up period inhibits the estimation of this effect over a longer duration.

In conclusion, this first meta-analysis assesses the pooled prevalence of infertility after CRC treatment. It provides clinically relevant information for fertility prognosis and patient counseling. Despite the low prevalence of gonadotoxicity in cases receiving chemotherapy alone, fertility preservation is still recommended due to the uncertainty of subsequent therapy and the lack of extensive, longitudinal data on individual treatment effects. Further prospective studies are needed to proof the individual impact of CRC treatment on gonadal function and to evaluate the effect of new treatment modalities, such as immunotherapies.

# **Author contributions**

M. von Wolff, S. Weidlinger, C. Anthon and A. Vidal designed the systematic review. T. Karrer prepared the templates for the literature search. The literature searches were performed by H Hecker, Eva Piccand, C. Anthon and A. Vidal. Data analysis was performed by J. Pape. Oncological advice was provided by M. Kornmann. The manuscript was written by A. Vidal and C. Anthon. All authors reviewed the final manuscript.

# **Acknowledgments**

We would like to thank the Swiss cancer league for funding the project and Irene Marcu for her support in the whole FertiTOX project.

# **Financing Information**

Financial support and open access funding were provided by the Swiss cancer league (Grant number: KLS-5650-08-2022).

# **Conflict of interest**

The authors have stated that there are no conflicts of interest in connection with this article.

# **Data availability statement**

# All the data utilized in the study are publicly available and/or contained within the manuscript or appendix.

# **Study registration**

# This systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO) under CRD42024511944.

# **Legends**

**Table 1** *Clinically significant gonadal toxicity definitions*

**Table 2** *Characteristics of the included studies* females

Summary of cohort studies assessing the prevalence of gonadal toxicity in women

**Table 3** *Characteristics of the included studies* males

Summary of cohort studies assessing the prevalence of gonadal toxicity in men

**Table 4** *Bias screening*

Newcastle-Ottawa Quality Assessment Form for Cohort Studies.

**Figure 1** *PRISMA flow* diagram

Flowchart of the literature search and selection process.

**Figure 2** *Pooled overall prevalence of general gonadal toxicity*

Forest plot of the proportions and 95% confidence intervals (CI) for the studies that evaluated the prevalence of gonadal toxicity in women and men following gonadotoxic therapy for CCR. Blue squares for each study indicate the proportion, the size of the boxes indicates the weight of the study, and the horizontal lines indicate the 95% CI. The data in bold and pink diamond represent the pooled prevalence for post-treatment infertility and 95% CI. Overall estimates are shown in the fixed- and random effect models.

**Figure 3** *Pooled overall prevalence of gonadal toxicity in women*

For details see legend of Fig. 2.

**Figure 4** *Pooled overall prevalence of gonadal toxicity in men*

For details see legend of Fig. 2.

**Figure 5** *Pooled overall prevalence of the gonadal toxicity subgroup for rectal cancer*

For details see legend of Fig. 2.

**Figure 6** *Pooled overall prevalence of gonadal toxicity among those who received chemotherapy only*

For details see legend of Fig. 2.

**Figure 7** *Pooled overall prevalence of gonadal toxicity among those who received radiotherapy only*

For details see legend of Fig. 2.

**Figure 8** *Pooled overall prevalence of gonadal toxicity among those who received the combination of radiotherapy and chemotherapy treatment*

For details see legend of Fig. 2.

**Table S1** *Database Search Strategies*

Systematic literature search in Medline, Embase and Cochrane CENTRAL.

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