Oncological treatments have limited effects on the fertility prognosis in testicular cancer: A systematic review and meta-analysis

Janna Pape[1], Jancy Fernando[1], Dimitrios Megaritis[1], Susanna Weidlinger[1], Angela Vidal[1], Frédéric D. Birkhäuser[2], Tanya Karrer[3], Michael von Wolff[1]

[1]Division of Gynecological Endocrinology and Reproductive Medicine, University Women´s Hospital, Inselspital Bern, University of Bern, Switzerland

[2]Urology St. Anna, Lucerne, Switzerland

[3]Medical Library, University Library Bern, University of Bern, Switzerland

Corresponding author:

ESHRE abstract: J. Pape

Paper: J. Pape

ABSTRACT

STUDY QUESTION: What is the prevalence of infertility defined by azoospermia, failure to achieve paternity or the usage of cryosperm after oncological treatments in testicular cancer?

SUMMARY ANSWER: The overall prevalence of infertility (95% CI) is 14% (9-21%) after all therapy types and 4% (2-10%) in a pooled subgroup of good-prognosis patients.

WHAT IS KNOWN ALREADY: Testicular cancer is the most common solid tumor among young men in the reproductive phase between 15 and 45 years. More than 95% of the patients become long-term survivors and up to 77% of cancer survivors report an interest in paternity after completing cancer treatment. Most guidelines recommend that physicians should counsel their patients about sperm cryopreservation before initiating gonadotoxic therapy. However, few studies have assessed fertility parameters after testicular cancer therapies over the last twenty years. Thus, this very first meta-analysis in a large pooled study population of patients functions as the best approximation of fertility prognosis so far.

STUDY DESIGN, SIZE, DURATION: The systematic review and meta-analysis is part of the FertiTOX project (www.fertitox.com) which aims to close the gap of data regarding gonadotoxicity of cancer therapies to enable more accurate counselling regarding fertility preservation. It was performed on all published studies since 2000 that have reported the prevalence of azoospermia, the failure to achieve a pregnancy over 12 months of regular unprotected sexual intercourse or the usage of cryosperm after oncological treatments of unilateral testicular cancer.

PARTICIPANTS/MATERIALS, SETTING, METHODS: A systematic literature search was conducted in Medline, Embase and Cochrane in December 2022. For the systematic review, studies with men after all types of unilateral testicular cancer were included. For the meta-

analysis, studies with unspecified treatments, < 10 patients for outcome evaluation or rare tumours were excluded. Infertility was defined as azoospermia, failure to achieve paternity or the usage of cryosperm. The quality of the individual studies was assessed using the Newcastle-Ottawa Scale.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 126 studies remained following screening of the abstracts and fulltext for the subject of the study. Of these, 30 studies including 13718 men with a history of unilateral testicular cancer were eligible and analysed for qualitative synthesis. Sample sizes ranged from 17 to 4846 patients with a follow-up from 1-30 (mean 6.5) years. Histology included seminomas (43.9%), non-seminomas (49.6%) and sex cord or stromal tumors (0.01%). Treatment comprised active surveillance after unilateral orchidectomy (32.7%), radiotherapy (23.1%), standard or low-dose chemotherapy (33.7%) and high-dose chemotherapy (1.4%). Spermiograms after treatment were analysed in 17 studies. A quantitative synthesis was performed in 23 studies. To account for heterogeneity observed among studies, a random-effects model was used to estimate the prevalence and its 95% CI. The overall pooled prevalence of infertility (95% CI) in men with unilateral testicular cancer after standard oncological treatment was 14% (9-21%). Azoospermia after all types of oncological treatments appeared in 8% (6-12%) of the pooled study population. For good-prognosis patients who received standard therapy (i.e. surgery with or without retroperitoneal lymph node dissection, low- or standard dosed platin-based chemotherapy up to four cycles and / or radiotherapy), the overall prevalence of infertility was only 4% (2-10%).

LIMITATIONS, REASONS FOR CAUTION: First, the majority of the studies based on either questionnaire or register data with evident selection bias. Second, further subgroup analysis was impossible due to predominantly mixed treatment cohorts allowing only an

approximation of standard therapy effects. Third, infertility might have occurred due to factors besides the oncological therapy.

WIDER IMPLICATIONS OF THE FINDINGS: Our meta-analysis includes all men with fertility outcome after testicular cancer therapy. Despite the overall low prevalence of infertility, sperm cryopreservation should still be recommended since it is unclear which therapy will follow after surgery and since there is no large longitudinal data for the various individual treatment effects.

STUDY FUNDING/COMPETING INTEREST(S): Public universities. No competing interests.

TRIAL REGISTRATION NUMBER: The study protocol was registered at the international Prospective Register of Systematic Reviews, PROSPERO (Registry number CRD42023384057).

KEY WORDS: testicular cancer, azoospermia, infertility, oncological treatment, fertility preservation