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ARTICLE

# Semen cryopreservation and usage rate for assisted reproductive technology in 898 men with cancer

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**Abstract** An undesired side effect of cancer treatment is potential subfertility or infertility. Timely cryopreservation of semen is the best modality to ensure fertility. This retrospective data analysis established the usage rate of cryopreserved semen from cancer patients. Pubertal and post-pubertal patients who could become infertile as a result of cancer (treatment) were offered the option to cryopreserve semen prior to treatment. Of the 898 patients who cryopreserved their semen in our hospital, 96 (10.7%) used this for assisted reproductive technology. The live birth rates for intrauterine insemination, in-vitro fertilization, intracytoplasmic sperm injection and cryopreserved embryo transfer were 13%, 29%, 32% and 17%, respectively. Of all couples involved, 77% achieved parenthood, i.e. 60 of the 78 patients (with complete follow-up) fathered at least one child.



**KEYWORDS:** assisted reproductive technology, cancer, cryopreservation, semen, usage rate

## Introduction

Although increasing numbers of patients survive cancer owing to improved treatment techniques (Edwards et al., 2014), an undesired side effect of these treatments is potential subfertility or infertility. Whether or not patients become infertile depends on the impact of the cancer itself on spermatogenesis (particularly in the case of testicular cancer,

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**Table 1** Risk of impairment of spermatogenesis after the use of cytotoxic drugs.

| *High risk* | *Medium risk* | *Low risk* |
|---|---|---|
| Cyclophosphamide | Cisplatin | Vincristine |
| Ifosfamide | Carboplatin | Methotrexate |
| Chlormethine | Doxyrubicin | Dactinomycine |
| Busulfan | BEP | Bleomycin |
| Melphalan | ABVD | Mercaptopurine |
| Procarbazine | | Vinblastine |
| Chlorambucil | | |
| MOPP | | |

(Data from Dohle GR, Int J Urol 1020; 3273–1). ABVD = adriamycin, bleomycin, vinblastine and dacarbazine; BEP = bleomycin, etoposide and cisplatin; MOPP = nitrogen mustard, oncovin, procarbazine, prednisone.

Hodgkin's lymphoma and leukaemia) (Hotaling et al., 2013), and the type, dose and duration of chemotherapy and/or radiotherapy applied (Dohle, 2010; Gandini et al., 2006; Meistrich, 2013; Trottmann et al., 2007) (**Table 1**). In addition, the psychological pressure of diagnostic workup itself may also depress sperm count. Thus early cryopreservation of semen is necessary. After a dose of 1.5–2 Gray (Gy) on the testis (despite gonadal shielding) permanent infertility usually occurs; partial recovery is possible after a dose of 1–1.5 Gy, whereas after a dose of <1 Gy fertility usually completely recovers within 14–22 months (Greiner, 1982). However, these numbers are subject to patient variation, and sperm motility recovery shows a high day-to-day fluctuation depending on the circumstances and the abstinence period.

Timely cryopreservation of semen is the best modality to ensure fertility. Although the duration of storage has no influence on sperm quality (Clarke et al., 2006; Horne et al., 2004), the process of freeze-thawing has a negative impact on sperm motility (O'Connell et al., 2002). Subak *et al.* illustrated this when reporting a pregnancy rate of 22% after intrauterine insemination (IUI) using frozen spermatozoa, in contrast to the much higher pregnancy rate of 48% using fresh spermatozoa ($P = 0.050$) (Subak et al., 1992). The thawed semen of cancer patients is often ineffective in achieving pregnancy by means of IUI. However, since the introduction of IVF in 1978 and intracytoplasmic sperm injection (ICSI) in 1992, it is possible to achieve pregnancy with low-quality spermatozoa (Palermo et al., 1992).

This study evaluated all recent studies that examined the usage rate of cryopreserved semen from cancer patients and the success rate of assisted reproductive technology (ART). Studies with a research population of ≥50 oncologic patients and a study duration of ≥10 years were regarded as relevant. The 13 evaluated studies (Agarwal et al., 2004; Bizet et al., 2012; Botchan et al., 2013; Chung et al., 2004; Crha et al., 2009; Freour et al., 2012; Hourvitz et al., 2008; Kelleher et al., 2001; Lass et al., 2001; Meseguer et al., 2006; Neal et al., 2007; Ragni et al., 2003; van Casteren et al., 2008) show a high success rate of ART, i.e. on average 52% of the couples achieved parenthood. However, despite this high success rate, on average only 7.5% (range 6–16.3%) of the cryopreserved semen was used. Moreover, only four of these 13 studies had a follow-up of ≥20 years (Agarwal et al., 2004; Botchan et al., 2013; Kelleher et al., 2001; van Casteren et al., 2008) and none has yet achieved a follow-up period of ≥25 years.

The aim of the present study was to evaluate the usage rate and effectiveness of ART performed with cryopreserved semen in a large group of cancer patients during 30 years of sperm banking.

## Materials and methods

### Patients and procedures

The study was performed at the University Medical Centre Utrecht (UMC Utrecht). In a retrospective analysis all oncological patients who banked their semen between 1983 and 2013, before undergoing treatment, were included.

Pubertal and post-pubertal patients who could become infertile as a result of cancer (treatment) were offered the option to cryopreserve semen prior to treatment. If cryopreservation was desired, the semen was obtained by masturbation and manually analysed according to World Health Organization (WHO) guidelines (World Health Organization, 1999, 2010). No morphology analysis was performed. The patients were advised to deliver an ejaculate twice. The semen was cryopreserved if motile spermatozoa were found. The semen was mixed at a 1:1 ratio with Freeze Medium containing human sperm preservation medium (until 1995) or TEST-Yolk buffer (Irvine Scientific, USA) (since 1995) and aspirated into IMV (Instruments de Médecine Vétérinaire) mini straws (IMV Technologies, France). The semen was frozen in a Planer Kryo560–16 freezer (Planer, UK) at a rate of 0.5°C/min to +5°C, followed by 10°C/min to −80°C, and finally stored in liquid nitrogen. All patients signed a form stating the terms and conditions for the cryopreservation of their semen.

Patients contacted the fertility physician if they wished to use their stored semen. The most appropriate ART method was chosen, taking into account the quality of the semen and the fertility of the female.

### Data collection

Data were collected from the patient's medical records in the hospital's central electronic registration system and the fertility clinic's specific data management system. The following data were extracted from the files of all participating men: date of birth, type of cancer, current health status (living, deceased/date of death), date of cryopreservation, and semen characteristics (volume, concentration, motility). If the cryopreserved semen was used, additional data were collected: date of use for ART, female age, type of ART (IUI, IVF, ICSI, cryo embryo transfer [cryo ET]), number of ART cycles, number of oocytes, fertilization rate, number of transferred embryos (in the case of IVF, ICSI or cryo ET), clinical pregnancies and live births. No information was available regarding the women's fertility.

The main aim was to determine how often cryopreserved semen of oncological patients was used for ART. The secondary aim was to determine the effectiveness of ART with cryopreserved semen of cancer patients in achieving