Fertilita’ dopo le cure

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- In an era of improving survival , fertility preservation after treatment for childhood cancer has become a central survivorship issue.

- Cancer treatments have improved considerably in recent years, giving pediatric cancer patients better chances of survival and consequently making it essential to try and assure these survivors a better future quality of life.

- Many studies have reported that infertility is associated with psychological distress and can have a negative impact on quality of life in cancer survivors .

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- Being able to have children could have an important positive effect on their future lives, and may be seen as a confirmation for these young people that they are normal and healthy again.
- The potential loss of parenthood has a profound impact on young women; the level of stress may be close to that of the cancer diagnosis itself.
- Furthermore, the sequelae of early loss of fertility in women (premature menopause) are clinically significant and include osteoporosis and cardiac diseases

- The potential for abnormal development, infertility, and sexual dysfunction is a source of significant emotional distress for male survivors

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Survivors after 5 years of follow up

’80→ 65%

’90→75%

- 300.000-500.000 long term childhodd cancer survivors in Europe

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- Established and experimental methods for preserving fertility have become available in recent years and cancer patients and their families show great interest in this topic.

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- In spite of this background there seem to be many barriers to fertility preservation in the pediatric hemato-oncology setting.
- For instance, several doctors do not discuss fertility issues at diagnosis with their patients, or within their families.
- Facilities for fertility preservation are variable between countries, within countries and even within single institutions

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Pancare Network spread a survey across Europe, assessing the availability of techniques' for fertility preservations :

- testicular and ovarian transposition,
- testicular and ovarian biopsy in pre-pubertal children,
- sperm and egg banking in post-pubertal individuals,
- hormonal treatments to protect ovaries from chemotherapy.

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Cancer survivors do not consider that they had adequate information, and some say that it was not possible to fully understand the implications of becoming infertile while at the same time, dealing with the diagnosis and treatment of a newly-diagnosed cancer.

Moreover, the quality of the information about infertility and possible preservation techniques received from pediatric onco-hematologist specialists could be very different compared to if these issues were discussed with patients by fertility experts .

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- Many articles have discussed the barriers encountered in efforts to deal with this issue, and the number of publications on the topic has increased in recent years.
- Some approaches to fertility preservation may involve delaying a patient's treatment or the need for different professionals to work jointly on a patient's treatment plan

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Recommendations based on scientific evidence are needed .

ASCO Guidelines for Children

- Use established methods of fertility preservation (semen cryopreservation and oocyte cyropreservation) for postpubertal minor children, with patient assent, if appropriate, and parent or guardian consent
- Present information on additional methods that are available for children but are still investigational
- Refer for experimental protocols when available

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- **Ovarian tissue cryopreservation and transplantation**.

- Ovarian tissue cryopreservation for the purpose of future transplantation does not require ovarian stimulation and can be performed immediately. In addition, it does not require sexual maturity and, hence, may be the only method available in children. Finally, this method may also restore global ovarian function.

- *However, it should be noted that further investigation is needed to confirm whether it is safe in patients with leukemias..*

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There are no specific suggestions as to which professionals should be involved, and no single group has been identified as being assigned the responsibility

- Despite all difficulties, a paper has reported that pediatric providers are more likely to discuss infertility with parents and patients compared to adult providers .

  Pediatric onco-hematologists understand the disease prognosis and are accustomed to speaking to patients/families with a serious illness.

  However, given their primary goal of treating and curing malignancies, pediatric onco-hematologists might stress the urgency of treatment , thus discouraging patients on fertility issues.

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Pediatric oncologist might avoid the issue because of uncertainty with regard to long-term prognosis.

Or they could lack extensive knowledge in fertility techniques

Or might underestimate the psychosocial impact of infertility and conclude that patients did not wish to discuss fertility.

→**In contrast, fertility specialists are likely to be unfamiliar with aspects of the disease.**

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- Information transfer from parents and their children plays an important role. This is a population of patients that will not recall having received any/or correct information about the potential impact on fertility.
- Young patients should be involved in a process of assent to treatment to the extent of their capacity although having children is something not yet imagined in adolescent patients and infertility risks may not be completely understood.

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- The different degrees of sexual development and the consequent different opportunities
- Time span available from diagnosis and beginning of treatment.
- The risk that cryopreserved ovarian tissue might contain malignant cells .
- Finally, the decision regarding the future use of cryopreserved tissue and posthumous reproduction: their legal and ethical consequences and are not yet defined .

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- It is essential to bear in mind that the provision of fertility preserving options needs to be planned and organized; it is not a simple matter and it may meet with various difficulties.
- It is important to talk to patients and their families about the cancer diagnosis, the type of treatment needed, the cure rates achieved, the late effects of treatments, and the risk of inherited cancer syndrome in progeny.

→ **The risk of infertility is one of the issues to discuss**.

- Recommendations on fertility preservation indicate that discussing the problems early on is crucial to future reproductive success
- ***But this is still only the starting point !!***

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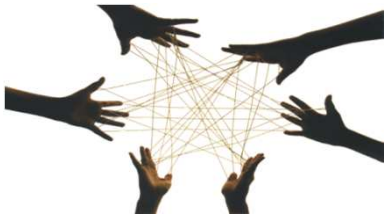
- Working at a cancer institute makes us responsible for filling the gaps in our knowledge in this area of patient care and drawing more attention to the growing importance of fertility preservation.
- In 2012 our institute started a cooperation scheme and developed a network with fertility preserving departments
- One of these was also equipped for processing and banking ovarian tissue.



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Patient's age, gender and pubertal status

- In prepubertal females, the only option is ovarian tissue collection, and this is recommended based on the gonadotoxicity of the treatment.
- Depending on the girl's age, the procedure was performed by a pediatric surgeon or a gynecologist using a laparoscopic approach.
- The ovarian tissue was collected by a biologist from the laboratory and a pathology report confirming the absence of malignant cells detected by histology was also produced.

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Patient's age, gender and pubertal status

- In postpubertal girls, the choice was between oocyte collection (a standard and effective procedure) and ovarian tissue collection (a promising option that is, however, still in the "experimental" stage).
- In pediatric age, the type of cancer-disease cannot be influenced by hormonal stimulation

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Post-pubertal males

- Sperm cryopreservation should be always suggested with a wide range of acceptance.
- However studies show that less than 25% of eligible male adolescents attempted to bank sperm.

Pre-pubertal males

- Tissue collection is still considered an experimental procedure and no clinical reports are yet available on the efficacy of this collection in humans

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The question of timing

- The usually rapid and symptomatic growth of pediatric malignancies does not allow us to delay the start of treatment for more than 7-10 days. This interval generally permits ovarian cortex banking.
- Oocyte collection may require longer, even if the recent development of random-start protocols (to allow the immediate start of ovarian hyperstimulation) now allows to reduce the time of collection to less than 2 weeks in most cases.
- For this reason, this the process should be fluent and efficient.
- In some part of our country could be difficult to find a center closer to the patient's home.

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General health status

- In the case of patients with symptomatic disease, it is sometimes advisable to start chemotherapy immediately, postponing any fertility preserving procedures until 1 or 2 cycles of chemotherapy have shrunk the tumor and restored the patient to a better general health status.
- Even if the preferred approach in fertility preservation is to collect materials prior to starting cancer treatment, this cannot always be done in clinical practice. Although we realize that collecting materials after treatment is not optimal , the richness of the ovarian reserve in the age group considered may, however, allow this strategy.

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Radiotherapy

- In patients prescribed radiotherapy to the pelvis, radiation oncologists estimate the treatment volumes and doses absorbed by the ovaries and uterus
- If necessary, they might suggest transposing one or both ovaries outside the radiation field, in which case ovarian tissue can be collected as part of the same laparoscopic procedure.
- The risk of radiotherapy-related damage to the uterus and its consequences for a future pregnancy is also explained to and discussed with the family.

Embryos need a cozy house

2016 J Gynecol Oncol

"Overall, current and future options should be discussed in a realistic and comprehensive manner with the woman, taking into utmost consideration that pregnancies require both the gametes and the uterus to take place. Embryos need a cozy house."

Somigliana E. et al

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Informed consent and costs

- Specific informed consent is needed for :

→the laparoscopic procedure,

→ ovarian tissue harvesting or oocyte collection, and for the related processing and banking.

- In Italy, the costs of all these procedures are covered by the National Health System, except for the pathology report and an annual banking fee.
- The social worker at our unit can discuss these aspects with a view to partially or totally covering such costs with funds from charities if the patient's family is unable to do so.

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Other Options

- We have also begun to test the administration of gonadotropin-releasing hormone agonists prior to commencing chemotherapy in postpubertal girls receiving chemotherapy; in such cases, the drugs administered have so far been off label and the expense borne by the patients' families.
- "*There is conflicting evidence to recommend gonadotropin-releasing hormone agonists (GnRHa) and other means of ovarian suppression for fertility preservation. The Panel recognizes that, when proven fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. However, GnRHa should not be used in place of proven fertility preservation methods.*"

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Post-Treatment Options

- In patients who survived the cancer and who are 17-18 years of age or older, the fertility expert may be called in to assess their risk of premature ovarian failure, any uterine damage caused by radiotherapy, and/or any need for preventive oocyte collection.
- Given the above-mentioned richness of the ovarian reserve in our age group, one may indeed consider banking oocytes after the end of treatment if the ovarian reserve is not severely compromised.
- However, this possibility of freezing eggs in childhood cancer survivors when they reach adulthood has received scant attention.
- It can overcome some of the limitations of ovarian cortex freezing (i.e the risks of surgery and to an iatrogenic insult to the ovarian reserve) and may be considered for girls scheduled for a chemotherapy at low or medium risk of ovarian reserve impairment.

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Post-Treatment Options

- It is relevant to mention here that women in the western world tend to delay seeking pregnancy, and that the ovarian reserve may actually get exhausted in cancer survivors prior to allowing them to fulfill their reproductive wishes .

  → **we need to stress this datum**

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Psychological aspects

- The multidisciplinary group should consider the favorable aspects but also emotional contraindications related to fertility preservation procedures.
- The maneuvers can be an implicit and important message of **hope** provided by physicians about the possibility of healing from cancer.
- At the same time, the scientific literature reports that the experience of not having been informed about the possibility to preserve fertility is accompanied by feelings of anger and depression
- However the proposal of an invasive procedure in addition to those necessary for cancer treatment can be experienced as an excessive burden by some young patients.
- Clinical experience has also shown the difficulty for some patients to think of a future pregnancy while they are in a phase of life and development in which such projects can be too early.

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The patient' Selection

- The practical consideration of the high costs of such procedures for the National Health System also raises the question of justifying the choice of not offering them to patients with a poor prognosis. Still different is the problem in countries where the costs are sustained directly by the patient and the family.
- The clinical, psychological, ethical and legal sense of a possible prognosis-related cutoff to decide whether or not to offer the preservation of fertility to a patient is something that remains to be well defined and established

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Most insurance plans do not cover **sperm banking**. The cost varies from one sperm bank to another.
The cost in the New York area ranges from about $700 to $1,300 for 3 collections, including the first year of storage. The sperm bank may also require that you have blood and urine tests for certain infectious diseases, which may add to the cost.

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Cost of egg and embryo freezing

- Freezing eggs and embryos is expensive, and unfortunately, most health insurance plans don't cover the cost. The cost is different at each fertility center but is generally about $12,000 to $15,000 for egg freezing and $15,000 to $18,000 for embryo freezing.
- These costs usually include the hormone medication, monitoring visits, egg retrieval under anesthesia, fertilization of the eggs (if creating embryos), freezing, and at least 1 year of storage. After that, the storage fee is about $1,000 per year. There are additional costs when you're ready to thaw and use the eggs or embryos to attempt pregnancy.

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Professionals involved

- A fertility expert
- A pediatric oncologist
- A surgeon
- A radiotherapyst
- A biologist
- A pathologist

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- Since September 2012, laparoscopy and cryopreservation of cortical ovarian tissue have been performed in the following diseases (patients' age→ range 2-20 years):
- Ewing family tumors ;
- medulloblastoma ;
- Wilms' tumors;
- non-Hodgkin lymphomas
- relapsing Hodgkin lymphomas
- relapsing CNS malignant germ cell tumors
- soft tissue sarcomas

  → **All patients were able to begin their chemotherapy 2-4 days after the laparoscopic procedure.**

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- *At diagnosis were perfomed:*

  - Ovary transposition, at the radiation oncologist's suggestion

  - According to the clinical condition, ovarian tissue was collected at the beginning or after several cycles of chemotherapy

  - Egg banking following ovarian hyperstimulation→ more than 20-day delay for the chemotherapy was considered too long by our standards.

- *After consulting the fertility expert, we observed:*

→ patients that refused any fertility preserving procedures.

→ pediatric oncologist that refused because of the risk of contamination by malignant cells;

- *For patients in follow up*:

→ some years after completing their treatments, oocyte retrieval and cryopreservation were performed.

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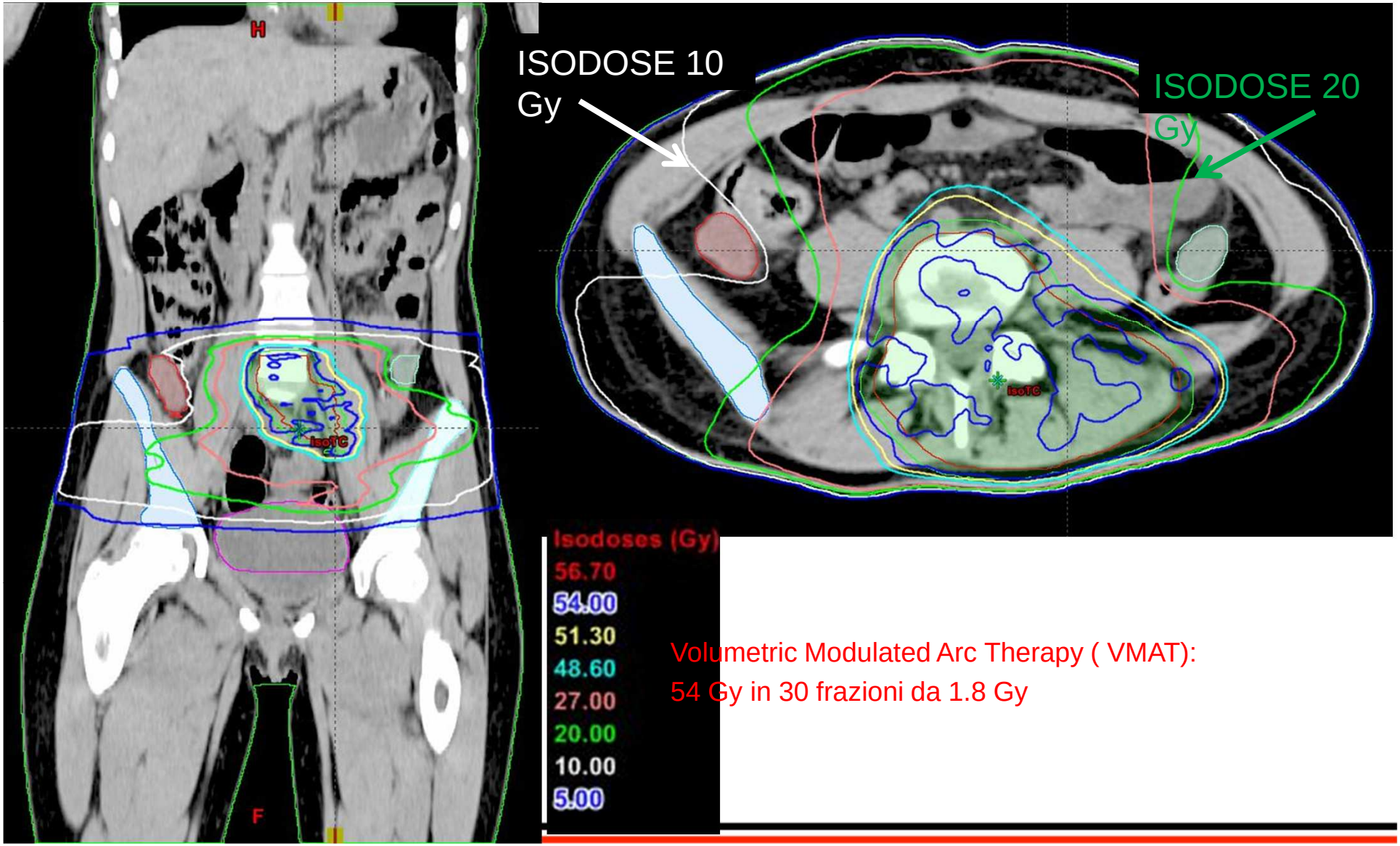
- It is unthinkable to simply provide information and offer the opportunity to choose a fertility preserving technique without accompanying families in their decisions on the matter and guiding them along a properly encoded path. Pediatric oncologists have to decide how much time there is to spare before starting chemotherapy, or whether it is better to delay ovarian tissue or oocyte harvesting until after the patient has had chemotherapy.
- Then it is up to the fertility professional to choose the best method for a given patient at a given time. For all these aspects to be handled adequately, it is fundamentally important to have a motivated team of specialists with good communication and capable of working together toward the same goal, which is ultimately to give patients the best chances of being cured of their cancer with the least possible iatrogenic sequelae.



Volumetric Modulated Arc Therapy (VMAT):
54 Gy in 30 frazioni da 1.8 Gy

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In conclusion, no single specialist appears to have all the skills required and a team combining these specialties might provide the best approach .
This area is challenging and rapidly mutable since fertility preservation is a work-in-progress area. This particular technology is quickly evolving and it may be more effective in the near future
However, it has to be faced now . We cannot wait for established conclusions since this will take years from now, in particular in pediatric patients.

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- Multidisciplinary care requires close communication and high levels of up-to-date professional expertise, and it is time-consuming because every single patient needs to be discussed in depth

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Grazie per l'attenzione

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