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REVIEW

Gynaecologic cancer surgery and preservation of fertility

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Summary For gynecological cancers, even at an early stage, the standard treatment is “radical excision” involving hysterectomy (radical or not) with bilateral salpingo-oophorectomy. But for young patients with early stage disease, many recent studies have focused on preservation of subsequent fertility by keeping at least one ovary and the uterus. The main objective of this fertility-sparing surgery is to preserve fertility, if this can be accomplished without increasing the oncological risks. Whether the initial site of the cancer is the cervix, uterine fundus or ovary, the oncologic validation of fertility-sparing treatment requires several evaluation criteria: a rigorous clinical, radiological and surgical staging to verify that the pathology is truly at an early initial stage; expert pathologic interpretation of biopsy specimens to validate the histological criteria of “good prognosis”; provision of complete and understandable patient education verifying the true objectives for this fertility-sparing treatment (whose intent is to retain a potential for subsequent fertility without guaranteeing it) and provision of an explanation of the oncological constraints and implications of fertility-sparing surgery in the event of a possible pregnancy. As always in oncology, this strategy demands teamwork requiring successive discussions with the patient and spouse and thorough discussion of the oncological safety of this fertility-sparing strategy in multidisciplinary consultation meetings before “giving a green light”.

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The particularity of gynaecological cancers is that they involve organs directly involved in reproduction. The currently employed treatments (surgery, radiotherapy, chemotherapy) often impact negatively on subsequent fertility. With better screening and improved treatment, more and more young patients are being diagnosed at an earlier

stage and cured, but simultaneously deprived of their fertility. Fertility must be considered as an integral part of the quality of life after cancer treatment.

When gynaecologic cancer develops in these young patients, it has major psychological implications, related not only to the announcement of a long and potentially fatal illness but also to necessary therapies that can result in definitive sterility.

To preserve fertility while treating gynaecological cancers requires the use of techniques, proven to have carcinological efficacy by different studies, with evaluation

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of remission, recurrence rate and overall survival rate. Several of these techniques [ovarian transposition, in vitro fertilization (IVF), oocyte freezing, cryopreservation of ovarian tissue than can be subsequently transplanted by ortho- or heterotopic autograft, and cryopreservation of ovarian tissue for in vitro maturation] have been evaluated and the patient and her partner can be informed of these options; these techniques are discussed in another chapter of this thematic issue.

Organ-sparing surgical treatment aimed at preserving the uterus and at least one ovary is increasingly finding a role in the management of early-stage gynaecological cancers in patients of childbearing age. Its purpose is to preserve the functionality of the reproductive organs by reducing the radicality of the surgical procedure, thereby allowing the possibility of a future pregnancy. The option of fertility-sparing surgical treatment is reserved only for selected cases that are defined by the stage, histology, grade and prognostic factors of the disease.

In this article, we will discuss the indications and modalities of fertility-sparing surgical treatment of the principal gynaecological cancers involving the uterine cervix, endometrium and ovaries. Pre-cancerous in situ or micro-invasive lesions of the cervix will not be discussed here and borderline ovarian tumours are discussed in another chapter of this thematic issue.

Cancer of the uterine cervix

Data in the literature concerning cervical cancer are numerous and rapidly evolving. More than 3000 cases of fertility-sparing treatment have now been published [1–21]. Selection of patients eligible for fertility preservation depends on precise staging of the lesion [clinical examination, lumbo-pelvic magnetic resonance imaging (MRI), expert pathology evaluation allowing definition of the histological type and the existence or absence of vascular emboli] and an evaluation of the patient's potential fertility.

Fertility-sparing treatment is oncologically acceptable only for cervical cancers smaller than 4 cm in size that do not require adjuvant treatment (no lymph node involvement). For some authors, the existence of vascular emboli is not an absolute contra-indication for uterine preservation, however their presence increases the risk of recurrence by about 10% [22]. A diagnostic cone biopsy has been proposed to improve the specific definition of tumour size and the existence or absence of vascular emboli [15]. All of the classical histological types (squamous, adenosquamous, and adenocarcinoma) can be managed with intent of fertility-sparing but the data on the mixed forms (poorly-differentiated adenosquamous glassy-cell carcinoma) are scant. However, neuroendocrine tumours are clearly associated with a greater risk of local recurrence and eventual metastasis, which absolutely contra-indicates fertility-sparing treatment. Five different technical procedures have been described whose indication depends on the size of the cervical lesion [22]:

- vaginal radical trachelectomy (VRT) was described by Daniel Dargent who was the promoter of this very innovative surgery. The procedure consists of resection of the entire cervix along with a 1–2 cm vaginal cuff, parametrium and para-colpos (akin to vaginal radical hysterectomy), while preserving the uterine fundus and anastomosing the uterine isthmus to the vagina [1–5];

- RT by laparotomy [6] (LRT);
- laparoscopic or robotically-assisted ‘‘minimally-invasive’’ RT (MIRT) [11–14];
- neo-adjuvant chemotherapy followed by fertility-sparing surgery (RT or cone resection depending on the surgical team [17–20]);
- and finally, cone resection alone [7–10,16].

Whatever the choice of procedure, lymph node staging (full nodal dissection or sentinel lymph node biopsy) is performed laparoscopically at the outset since lymph node involvement makes fertility-sparing surgery less acceptable oncologically. The choice of one of these techniques does not always correspond to principles established by ‘‘evidence-based medicine’’ or on well-defined oncological strategic principles, but more often on very subjective elements such as the habits of the surgeons who specialize in these techniques and on their own beliefs about the advantages of one technique over the others. In order to better analyze the oncological results of these interventions in terms of fertility, we recently performed an exhaustive review of the different series in the literature [22,23]. Fig. 1 and Table 1 summarize these data. We reviewed nearly 160 articles, involving more than 3100 fertility-sparing surgeries. VRT is indicated only for cancers smaller than 2 cm because the 17% risk of recurrence for larger tumours is not carcinologically acceptable [22]. The oncological need for parametrial resection is debatable for cervical cancers smaller than 2 cm without vascular emboli. For such cases, a simple trachelectomy or conization could be envisaged as long as oncologic safety can be guaranteed by clear resection margins of at least 8 mm. The risk of recurrence in this context is < 0.5% (Fig. 1, Table 1) [22]. Nevertheless, since only a limited number of cases have been reported with this strategy, cohort studies or additional studies are essential before this gesture can be validated for routine use in tumors < 2 cm without vascular emboli. For tumors < 2 cm with some vascular emboli, VRT might also retain its potential indication (Table 1) [22].

In stage IB-1 cervical cancer > 2 cm where VRT is contra-indicated, two strategies can be proposed: neo-adjuvant chemotherapy followed by organ-sparing surgery, or abdominal trachelectomy (LRT or MIRT) with a more extensive radical paracervical and paravaginal dissection than can be performed by the trans-vaginal route. Oncological outcomes are similar with a recurrence rate between 6% and 7% [22], but abdominal surgery has the disadvantage (especially when performed by laparotomy where the risk of adhesions is increased) of frequently requiring ligation of uterine artery branches that may potentially impair subsequent fertility [23]. Pregnancy rates are lower after LRT than after chemotherapy followed by fertility-sparing surgery (Table 1) [23]. The rate of premature delivery is also higher after laparotomy (Table 1) [23]. In addition, severe septic complications and two cases of uterine necrosis have been reported after abdominal LRT [22]. As a result, first-line chemotherapy followed by fertility-sparing treatment seems preferable to LRT for stage Ib-1 cervical cancer > 2 cm; the carcinological results are equivalent but the first option has improved fertility and fewer major complications. The use of a minimally-invasive abdominal approach (MIRT) seems to improve the pregnancy rate (Table 1) [23]. We do not yet have sufficient data to compare this neo-adjuvant chemotherapy strategy versus MIRT (whether purely laparoscopic or robot-assisted).

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