Organ and Fertility Preservation in Gynecological Cancers

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Introduction

Quality of life has become a very important factor in deciding the extent of surgical procedures for patients affected with a variety of cancers. In recent years attention is being focused on preserving organ function, cosmesis and fertility potential. As the survival rates have increased with improved treatment of cancer, the patients are more interested in preserving their reproductive function.

The primary end point of cancer treatment is cure. However, the radicality of cancer treatment can lead to impaired sexual and reproductive function, unacceptable cosmetic appearance, altered body image, severe impairment or loss of organ function and a variety of long term side effects which can have a significant negative impact on the self esteem and the psyche of the patient. This, in addition to the psychological impact of suffering from cancer, can lead to serious loss of quality of life of these patients.

With the emergence of effective alternative non-surgical treatment modalities in recent years and with better understanding of the disease, there has been a dramatic paradigm shift in the radicality of surgery for many cancers – leading to organ and function preservation with a better quality of life, without compromising on survival. With better understanding of the biological behaviour and mechanisms of spread, the surgeries for cancer, at many sites, have been downscaled without affecting the end-results. In the gynecologic oncology too, many new and innovative techniques and approaches have been devised to treat gynecological cancer, aiming at preserving fertility potential.

Radical trachelectomy for cervical cancer

It is estimated that 10-15% of cervical cancer cases are

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presently diagnosed in young women in the child bearing years, in whom removal of uterus will deprive them of an opportunity of having babies[1]. Although alternative reproductive options like in-vitro fertilisation with embryo cryopreservation and gestational surrogacy are still available to these women, they are complex, expensive and often ethically not acceptable[2]. Thus, the radical trachelectomy procedure which allows preservation of the body of the uterus, thereby preserving reproductive function seems to be a significant advance in the management of these young women with cervical cancer. This procedure was first described by Dargent et al[3]. The initial skepticism about it is slowly being replaced by acceptance and optimism. Tachelectomy is usually preceded by a laparoscopic pelvic node dissection and on confirmation of absence of metastatic involvement of lymph nodes, trachelectomy is proceeded with. It is essential to confirm adequate disease free margins after trachelectomy by frozen section examination. If adequate margins cannot be obtained, a complete radical – vaginal or abdominal hysterectomy is required.

The recently published results of radical trachelectomy from four centres show that the majority of the patients undergoing this procedure had squamous carcinoma of stage IB-1 or less without vascular space invasion and 2 cm or less in size 4-7. The overall recurrence rate in these four published series is 3.1% (4 of 130 patients), which is similar to the one reported after radical hysterectomy. Covens et al[6] compared their patients with two series of matched patients with standard radical hysterectomy and demonstrated equivalent survival. The two year actuarial survival for their patients was 95%. Since there is a two to five percent chance of pelvic node metastases even with small cervical lesions selected for trachelectomy, pelvic lymphadenectomy is an essential part of the procedure.

The obstetric outcome in the reported data has also been encouraging. Totally, 49 pregnancies in 36 women have been reported; they resulted in 26 live births. Although there was a concern about the potential infertility problems consequent upon shortened cervix and inadequate mucus production, most of the pregnancies were natural i.e. without assisted reproduction methods.

Covens et al[6] reported that all women in his series, who attempted conception, became pregnant within 12 months, giving a conception rate of 37% at one year. It is interesting to note that three of their patients who conceived had a prior history of infertility, indicating that such a prior history need not be a contraindication to radical trachelectomy. Most women delivered by cesarean section. All authors have reported increased incidence of premature labor, probably due to chorioamnionitis consequent to inadequate mucus plug. To overcome this problem, Dargent et al[4] have been performing the Saling procedure at 14 weeks, wherein the external os is covered with vaginal mucosa to prevent ascending infection.

Although the oncological and obstetric outcome appears to be favorable and the morbidity of the procedure is low, the number of patients who have undergone this procedure is still small. This procedure needs to be tested in a prospective randomized trial with a larger number of patients in order to define its exact role. Yet, this procedure may offer an important treatment option to those young women with cervical cancer who wish to preserve their fertility.

Endometrial Cancer

Total abdominal hysterectomy with bilateral salpingo-oophorectomy is the standard treatment and is well accepted since the majority of endometrial cancer patients are post-menopausal. However, approximately three to five percent of all endometrial cancers occur in women below the age of 45 and rarely in even younger women below the age of 25[8-11]. These women may wish to preserve their fertility potential without compromising on cure. Many of them have chronic anovulation, irregular menses, obesity and polycystic ovaries[9,11,12] although it is not essential to have these risk factors in order to develop endometrial cancer[8,13]. In fact, the diagnosis of endometrial cancer is often made in these young women during the course of investigations for infertility. It is also important to inquire into the family history of these patients since they can be a part of a Lynch II syndrome family[13,14]. It is important to define a conservative approach in these women in order to preserve their fertility.

A majority of these women have well differentiated cancers with little or no myometrial invasion and excellent prognosis with survivals exceeding 95% as reported in the GOG data[15]. High doses of progesterone have been used to reverse the adenocarcinoma process in these women desirous of child bearing. This was based on the early work done by Bookman et al[16], who demonstrated reversal of well differentiated carcinomas in 24% of women who were given a short course of progestins prior to hysterectomy. Currently, there is a growing body of literature indicating that in certain selected cases, it is possible to use conservative management with the use of progestational agents.

Although there is no consensus regarding the best progestational agent to use and although the optimum dose and duration of therapy has not been defined, megestrol acetate in the dose of 40-160 mg per day is the most frequently used agent[17,18]. Concomitant use of tamoxifen has been proposed by some to prevent the possible down-regulation of progesterone receptors by the continuous use of progesterone and also because tamoxifen can stimulate progesterone receptor production[16,19]. Most of the complete reversals appear in the first 3-6 months of treatment and it is of utmost importance to regularly monitor response to therapy regards with dilatation and curettage at three to six months intervals. In case of partial response, the therapy may be continued longer, even more than a year, in order to elicit a complete regression[16,20]. Women with persistent disease, however, warrant a prompt hysterectomy[17]. In all, about 50 to 75% of women with well-differentiated adenocarcinomas respond well to progestational agents and a majority of these responses are durable.

Following reversal of carcinomatous changes with progestins, successful pregnancies have been reported, a majority of them naturally soon after reversal of their cancer[12,18,19,21,22]. In some cases, where the underlying infertility problem has persisted, some authors have used ovulation induction with clomiphene citrate and even IVF to achieve pregnancy[18,21-24]. Ovulation induction appears to be safe and there is no evidence of increased cancer recurrence risk with its use, although the follow up in most series is short. Besides, most of these women have been reported to be disease-free to date.

Conservative treatment of endometrial cancer, though appealing, is not without risks. There is a significant risk of underestimating the extent of disease based only on clinical examination. In view of this, additional investigations e.g. transvaginal sonography, hysteroscopy, laparoscopy, MRI, CA-125 etc. have been suggested to more accurately stage the patient clinically and to document myometrial or metastatic spread[12,18-25]. Besides, several authors have reported 16 to 29% incidence of synchronous ovarian and endometrial neoplasia or ovarian metastases[8,17,26,27]. This necessitates the use of proper pelvic evaluation by means of imaging studies or laparoscopy prior to initiation of conservative treatment. Conservative treatment may also delay the potentially curable definitive treatment, with increased

potential for recurrence or progression to metastatic disease. Although the risk of disease progression during or after progesterone therapy is only about five percent[12] the follow up in most series is short which may result in underestimation of the true progression rate. More data with longer follow up is needed before definite recommendations can be made regarding the safety of the conservative approach. Definitive hysterectomy after completion of child bearing seems to be logical but may not be essential since most of the responses after progestational therapy appear to be durable.

Epithelial ovarian cancer

Approximately 3 to 15% of patients with epithelial ovarian cancer are younger than 40 years of age at the time of diagnosis and nearly eight percent of all stage I epithelial ovarian cancers occur in women less than 35 years of age, in whom fertility preservation may be an important issue.

The standard treatment for early stage ovarian cancer includes total abdominal hysterectomy with bilateral salpingo-oophorectomy. Conservative surgery may be offered to selected patients with stage I A grade I-II cancers wishing to preserve their fertility, if adequate comprehensive surgical staging has been performed in them. Frozen section facility is essential to rule out advanced disease intra-operatively. The criteria for conservative surgery in patients with early stage ovarian cancer have been defined by McHale and DiSaia[28]. In patients in whom the disease is truly limited to one ovary, prognosis is excellent and conservative surgery may be advised in suitable patients. Even in stage IB patients, uterus may be preserved to permit pregnancy by accepting ovum donation.

The risk of occult malignancy in contralateral ovary is quite low, in the range of five to seven percent[29]. Routine biopsy of apparently normal looking ovary is not recommended since microscopic foci of cancer can still be missed and it can lead to iatrogenic adhesions and infertility[28]. Recent studies have shown that the recurrence rate for patients undergoing conservative surgery is not different from those undergoing radical surgery[29,30]. Since both these studies included patients with stage IC disease, it is proposed that the indications of conservative surgery may be expanded to include patients with stage IC disease. However, this is highly controversial, and the long term results need to be assessed in a large number of patients before such recommendation can be made. Conservative surgery has no role in patients with advanced epithelial ovarian cancer.

Successful obstetric outcome has been reported after conservative surgery. However, the chance of successful pregnancy is reduced after adjuvant chemotherapy due to premature ovarian failure in some women. There is no consensus on the need for removal of the other ovary after childbearing, but it appears to be preferable[29,30]. It is essential to counsel the patients for conservative surgery regarding all these factors pre-operatively.

With more widespread use of laparoscopic techniques in the surgical treatment of ovarian cancer, it remains to be seen whether the fertility rate will improve due to lesser surgical tissue trauma and reduced adhesions.

Borderline ovarian tumors (Tumors of low malignant potential

Conservative surgery can be safely offered to patients with borderline tumors. The majority of borderline tumours are diagnosed in stage I, are uncommonly bilateral except in the serous variety and have excellent prognosis with a very low relapse rate of less than five percent[31]. Besides, comprehensive surgical staging in apparently stage I tumors is not mandatory because of the low yield of upstaging and chemotherapy is rarely, if at all, used in the management of these tumors[32]. These patients can be treated effectively with unilateral salpingo-oophorectomy. Tazelaar et al[33] found no evidence of microscopic disease in grossly normal ovaries that were bivalved in 61 patients with stage I low malignant potential tumors of the ovary. In the literature, some patients with borderline epithelial ovarian cancer have been treated with ovarian cystectomy with preservation of normal ovarian parenchyma, with recurrence rates equivalent to those after salpingo-oophorectomy[34,35].

Excellent fertility has been reported in patients with borderline tumors who have undergone conservative surgery. Ovulation induction and IVF have been used with good success rates in patients unable to conceive naturally[35,36].

Germ cell tumors

These are highly curable ovarian neoplasms, seen predominantly in young women. Since they affect the childbearing potential, appropriate management by specialists is mandatory. Germ cell tumors, irrespective of their histologic subtypes, are extremely chemosensitive, even in advanced stages. This allows conservative surgery to be carried out effectively in these patients. Most patients can have their fertility preserved and the type of operative procedure depends on the intraoperative findings. In most cases, the contralateral ovary and uterus can be preserved[37]. Germ cell tumors with the exception of dysgerminoma are rarely bilateral. Even in patients with dysgerminoma, bilateral

oophorectomy is rarely necessary because adjuvant chemotherapy is highly curative and fertility can be safely preserved[38]. In cases where the contralateral ovary is grossly abnormal, cystectomy or removal of cancer-bearing tissue with preservation of normal ovarian tissue can be attempted. Even in the presence of widespread metastatic disease, the contralateral ovary and uterus can be usually preserved, thanks to the efficacy of chemotherapy.

Cancer of the vulva

The most significant advance regarding conservation in gynecologic oncology is seen in vulvar cancer, where the cosmetically and functionally compromising procedure like radical vulvectomy with groin node dissection is now almost never advocated.

Way[38] established that a very wide resection of vulvar lesion was vital to the chances of cure from cancer of the vulva and therefore radical excision was performed even for small tumors. However, this led to devastating mutilation especially in young patients and compromised the cosmesis and sexual function, besides causing serious alternations in body image. This provided a stimulus for developing an alternative and conservative approach to early vulvar cancer, which aimed at conservation of body image and sexual function by retaining large areas of vulvar tissue including mons veneris and clitoris whenever possible[40]. Conservative surgery can reduce sexual dysfunction and urethral/anal problems, while local control and survival are not compromised. Surgery is now almost always limited to ipsilateral wide local excision in case of small lateral lesions[41].

Today, an individualised approach is advocated by most for treatment of early invasive vulvar cancer[42-47]. Most T1 and selected T2 lesions can be controlled with a radical wide local excision. A wide and deep excision of the lesions is performed with the incision deepened down to the inferior fascia of urogenital diaphragm and/or pubic periosteum. An effort should be made to remove the lesion with a 2 cm margin or normal tissue in all directions unless this requires sacrifice of urethra or anus. Heaps et al[48] suggested that although it has been customary to aim for 2-3 cm margin, a minimum of 1 cm might be adequate. Small T1 lesions that invade 1 mm or less may be managed by local excision alone because the risk of regional spreads is low. Patients with more invasive lesions must have a concomitant treatment of groin nodes.

The major deterrent for conservative surgery is the multicentricity of invasive cancer in 20-30% cases. However, Hoffman[49] (1992) demonstrated that conservative surgery led to local control and survival comparable to that with radical vulvectomy in well selected patients. Other authors have also shown that these conservative approaches result in survival comparable with that after more radical operations and fears of an increased local recurrence rate as a result of less radical surgery are unwarranted[42-48,50].

Conclusion

Surgery for several cancers has now become less aggressive with more emphasis on preservation of functioning organs and quality of life. With more and more women in the childbearing age being diagnosed with gynecological cancers, fertility preservation has become an important issue in young women afflicted with these cancers. This has resulted in redefining their treatment. Although the conservative approach appears to be justified in well-selected patients, it remains to be seen how much these indications for conservative surgery can be expanded without jeopardizing the survival of these patients. It is imperative, till such time, that only those patients fulfilling the criteria based on current evidence are offered conservative surgical approach.

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