EDITORIAL

New directions in gynaecologic oncology

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Gynaecologic oncology is a new branch of gynaecology that has become a subject of intense clinical and basic research. Many of the gynaecologic malignancies today have a high 'cure' rate. This can be attributed to the development of diagnostic techniques that can identify precancerous conditions, a better understanding of patterns of spread, and the development of effective treatment modalities in these cancers that previously had a very poor prognosis. Whilst new treatment strategies are being devised some traditional concepts are being challenged.

FIGO staging

Staging in gynaecologic malignancies is based on the International Classification adopted by the International Federation of Gynaecology and Obstetrics (FIGO). Although this has been revised from time to time, the last being in 1988, diseases of wide variability are often included under one subheading; such a classification will be only of rough prognostic value if further modifications are not made.

Carcinoma Cervix

A few controversial issues have arisen with respect to cervical carcinoma. Firstly, stage IA_1 disease has been defined as minimal microscopically evident stromal invasion; the exact depth of invasion is not clearly defined, thus leaving room for interpretation that is not uniform. Secondly, stage IA_2 has been defined as measurable stromal microinvasion up to 5mm deep from base of epithelium, either surface or glandular, and a second dimension, the horizontal spread, not exceeding 7mm. Most institutions, such as ours, will consider stage IA_2 as microinvasion not exceeding 3mm depth; the incidence of lymph node metastases in lesions with invasion of 3.1 to 5mm depth has been reported to be 4.8%[1]. These latter group of patients are best treated by radical surgery.

Thirdly, survival in stage 1B disease is influenced by a number of factors. Although a clinically obvious 0.5cm lesion carries the same stage as a 6cm lesion, the prognosis in patients with large bulky disease is poor whether treated by surgery[2] or radiotherapy[3,4]. The most dependent variable associated with survival is the lymph node status. In our experience[5] patients with negative nodes have a 5-year survival of 95.5%; survival in those with 2 positive nodes or less and more than 2 positive nodes are 80.5% and 68% respectively. Others report survival for those with positive nodes ranging from 20% to 60% depending on number of nodes, the location and site of merastases[6-9]. Patients in whom the depth of invasion is <1.5cm have a 5-year survival of above 90% but this falls to less than 78% if the invasion exceeds 1.5cm[10,11]. The presence of lymphatic/vascular space permeation reduces the survival rates to 60-70%[12,13]; even in the absence of lymph node metastases, many cases have been reported to recur[14]. Where undetected parametrial extension occurs, the 5-year survival is only 69% compared to 95% when the parametrium is negative[15]. Clearly, if staging is to reflect the true prognosis

of the disease, these important prognostic factors evaluated histologically need to be incorporated into the guidelines.

Fourthly, clinical assessment of parametrial extension in cervical carcinoma can be deceptive. In one study[16], 66% of cases clinically staged as 2B disease had no evidence of parametrial extension in the operative specimen.

Vulval Carcinoma

The staging takes into consideration tumour size, extension to surrounding structures, presence or absence of regional nodal metastases and distant spread. A tumour 8-10 cm size often has a worse prognosis than a 2-3 cm size tumour; similarly prognosis will also be dependent on the size and number of metastatic nodes involved; the inclusion of these important variables needs to be looked into.

Endometrial Carcinoma

The staging is clinical, based on careful clinical examination and a limited number of pre-operative investigations. Understaging occurs in 5-20% of cases with stage I disease[17,18]; 40-50% of stage 2 cases are overstaged[19,20]. Further, extension of the endometrial carcinoma to the cervical stroma may be missed in the absence of surface involvement[21]. Clearly surgical/histological evaluation is important in staging.

However, in patients who are 'inoperable' because of 'medical problem', clinical staging would appear sufficient.

Carcinoma Ovary

Ovarian carcinoma is staged surgically; the most appropriate incision is a lower vertical abdominal incision that extends above the umbilicus to allow adequate evaluation of the whole abdominal cavity to carry out optimal tumour debulking. Perhaps the most controversial area is with Stage 3 disease. The FIGO Classification refers to the pre-operative tumour size and extent of disease. We do know, however, that the prognosis in this stage is mainly influenced by tumour size remaining at the end of surgery; it is currently felt that the residual tumour size of 0.5 cm or less if needed for optimal results. Thus, this stage needs to be revised.

In patients with large fixed bulky disease optimal cyto-reductive surgery may not be possible. Neo-adjuvant chemotherapy may make subsequent surgery easier. In these instances as surgical staging prior to therapy is not possible, one will have to rely on clinical, ultrasound and if available CT and MRI findings.

Early diagnosis

Pap smear screening and the use of colposcopic examination have contributed immensely to the early disgnosis of pre-invasive and early invasive of the cervix. Recently Coppleson et al[22] have devised an electronic cerviprobe which picks up electrical characteristics when in contact with abnormal cervical cells; these are then transformed and categorised by an electronic instrument to emit an audio-signal. This instrument shows promise as an instantaneous detector of cervical cancer and its precursors.

For overian cancer, on the other hand, no significant inprovements have been made in its early diagnosis. Apart for germ cell tumours, tumour markers are of little use in the early diagnosis because of lack of specificity and sensitivity although these have a place in the follow up of patients. Recently vaginal ultrasound and colour flow imaging have been used for screening;[23] although these have

significant false positives, with further improvements these may have an important role in screening of "high-risk" patients.

Therapy

Cervical Cancer

Surgery will continue to play an important role in the management of early invasive cancer of the cervix particularly in young patients where ovarian and coital function can be preserved. When 'high-risk' factors are present the prognosis is poor[5-15]. We have obtained in these 'high-risk' group of patients disease-free survivals approaching that of patients without 'risk' factors[24,25]. Similar results have been reported by others[26]. It appears that when 'high-risk' factors are present cervical carcinoma is behaving like a systemic disease where local treatment alone is not sufficient. Thus, in the years to come adjuvant chemotherapy can be expected to have an important role in the surgical management of early invasive cancer of the cervix.

Chemotherapy is also playing an important role as neo-adjuvant in larger bulky cervical lesions. Our initial experience with Mitomycin C and 5-fluorouracil in these patients has been encouraging with complete responses in 2 cases, and considerable tumour reduction in 8 others; in only 2 patients was lymph node metastasis (one each) present[27]. Such reduction in tumour size facilitates surgery. Neo-adjuvant chemotherapy has also a role in overall survival in patients with advanced disease prior to radiotherapy.

Ovarian Cancer

Surgery continues to be the main modality of treatment in this condition, however advanced or aggressive the tumour is. There are 4 sub-groups of surgery that can be carried out - primary surgery, 'second-look' surgery, re-exploration and salvage surgery.

The vast majority of patients are already at an advanced stage of disease at presentaiton. The aim of surgery should be to remove all of the tumour that is possible and reduce it in size in order to obtain greater response to chemotherapy[28]. Achieving a 2 cm residual tumour size or less was at one time thought to be important; it is now felt that for optimal results this should be reduced further to less than 0.5cm. The Cavitron ultrasonic surgical aspirator has been found to be particulary useful in debulking disphragmatic and liver capsule metastases[29]. Difficult resections of overian carcinoma have been facilitated by the Nd:YAG laser[30]. Recently the argon beam coagulator (ABC) has been shown to enable debulking of ovarian cancer in sites inaccessible to conventional resection[31]. A recent study claimed up to 90% 5-year survival with stage 3 and 4 ovarian cancer if optimal primary surgery left no macroscopic disease[32].

Attention is now being directed at routine para-aortic and pelvic lymphadenectomy. One-third of women with stage I disease do not survive[33]. The disappointing results may be due to the presence of sub-clinical para-aortic micrometastases not identified at the initial staging laparotomy and are in fact occult stage 3 cases requiring aggressive adjuvant chemotherapy. The incidence of para-aortic node metastases in apparent stage I disease in 12.2%[34]. Positive retroperitoneal nodes occur in 70% of patients with stage 3 disease; Burghardt et al have reported that extensive para-aortic lymphadenectomy is of therapeutic benefit[35,36].

The role of this procedure in the surgical management of ovarian cancer, however, remains controversial. Perhaps the intraoperative use of an instrument similar to the recently introduced electronic cerviprobe[22] has potential in selecting those patients with positive nodes for this procedure. Until then gynaecologists will continue to carefully assess the retroperitoneal nodes by palpation, sampling suspicious nodes and removing large nodes as part of a debulking procedure.

Second-look procedures in ovarian cancer remain controversial. Since the 1970s these became widely incorporated as part of the primary radical therapy for management of epithelial ovarian carcinoma. The complication rate from this procedure is as high as 63%[37]. Non-invasive techniques such as ultrasonography, computed axial tomography, magnetic resonance and radioimmunolocalization have significant false-negative rates and remain less sensitive than a laparotomy for the detection of small volume macroscopic disease[38-41]. Attention has been directed to the use of *serum markers.* Currently CA125 has shown the greatest promise. However, as up to 50% of patients with negative values will have residual disease of up to 2cm diameter at second-look procedures, CA125 lacks sensitivity and is inferior to second-look surgery in sub-clinical disease[42,43].

A review of the literature shows that 4-53% of patients who had histologically negative second-look procedures subsequently recurred; thus the second-look laparotomy provides limited prognostic information.[44-48]

Recently, *neoadjuvant* chemotherapy has been used in patients with advanced, fixed tumours. Whilst optimal secondary surgery is possible after a completed course of chemotherapy, the results have been poor; this has been attributed to the development of chemoresistent clone of cells. To overcome this, early secondary cytoreductive surgery has been suggested during primary induction chemotherapy[49]. This needs further evaluation.

In the young patient, treatment needs to be individualised. Conservative surgery is possible in patients with advanced germ cell tumours thus allowing fertility to be preserved[50].

Vulval Carcinoma

In recent years as patients have tended to present with earlier stage disease, conservative surgical procedures for vulval carcinoma have been advocated. As multicentricity has been reported to occur in 20 to 26% of invasive squamous cell carcinoma of the vulva[51,52] the chief concern of such a procedure would be the increased risk of local recurrence. Hacker et al[53], however, found a local recurrence rate of 4% when superficially invasive carcinomas were treated by wide local excision alone which was similar to those who underwent radical vulvectomy. Thus, in selected stage 1 patients wide local excision appears to be an appropriate modification of treatment that will help reduce sexual dysfunction and disfigurement.

For lesions >2cm diameter and those stage I patients where depth of invasion exceeds 1 mm, the most important modification has been to use separate incisions for the groin dissection[53-55]; this will allow closure without tension and thus decrease norbidity. Fourteen to twenty-one per cent of patients managed in this manner experience significant groin wound breakdown[53,56].

In the surgical management of locally advanced vulval cancer, radiotherapy has a useful adjunctive role. Firstly, post-operative irradiation of the groins and pelvis help decrease recurrences at these sites when inguinal nodes are positive[57]. Secondly, pre-operative chemoradiation in advanced inoperable tumours will allow a more conservative surgery in patients who would otherwise need pelvic exenteration, which carries a high mortality and morbidity[58,59].

In patients who are young, the use of flaps (gracilis myocutaneous tensor fascia lata fasciocutaneous or the tectus abdominus musculo-cutaneous flap) have the potential to close these defects for improved function and appearance[60,61].

In the modern management of vulval carcinoma treatment must be individualised. In doing so the curative potential of therapy should not be sacrificed; modifications that reduce morbidity whilst retaining curative potential are needed.

Trophoblastic Disease

The malignant potential of *partial* moles has now been recognised and these require close follow up examinations as for complete moles[62,63]. The treatment of gestational choriocarcinoma is primarily chemotherapy. Radiotherapy has a limited role, in patients with brain metastasis for instance. With the availability of effective chemotherapeutic regimens, good survival can be obtained even in advanced disease. In resistant cases, the use of ultrasound, CT, MRI and radio-immunolocalization with anti-HCG antibodies can help identify sites of persistent disease which can be surgically removed. Therapeutic approaches with radiolabelled monoclonal antibodies and antibodies coupled to metabolite-depleting enzymes are being tried[64].

Conclusions

Several new advances have been made in all modalities of management of gynaecological malignancies. To reduce the systemic effects of chemotherapy, *regional drug delivery* appears ideal for selective action at *target sites*; local intra-arterial perfusion of drugs and coupling of drugs to specific monoclonal antibodies would be ideal and are being explored.

Current trends are promising. With *individualised* management the gynaecological patient can look towards successful treatment and longer survival.

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