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EORTC Report

The Present Role of Laparoscopy in Gynaecological Oncology; the EORTC Point of View

J.B. Trimbos and P. Zola

INTRODUCTION

THE HISTORY of laparoscopy began in Europe. Pioneers like Raoul Palmer developed relevant methods that made diagnostic laparoscopy feasible and safe. In the years after World War II, the pneumoperitoneum and the Trendelenburg position became an integral part of clinical laparoscopy.

For decades, gynaecological laparoscopy remained a diagnostic tool for infertility and pelvic pain and it was used for sterilisation. Recently, there has been a new interest in laparoscopic surgery (LS) by the general surgeons exploring laparoscopic gallbladder removal and colonic procedures. With this revival, new applications in fertility surgery and benign gynaecology have been developed and at present a new procedure in gynaecological laparoscopy seems to emerge every few months. Laparoscopic procedures have also been undertaken in the field of gynaecological oncology, but "the proliferation of endoscopic procedures seems haphazard, uncontrolled and dominated by a few endoscopic virtuosos, with more interest in the technical development of new instrumentation and capabilities for operative laparoscopy than in the methodical integration of this exciting technology into the discipline of gynaecology" [1]. This integration is difficult by its very nature because survival is ultimately at stake in oncology, and a jeopardised survival is an unrealistically high price for decreased morbidity.

The present situation is that laparoscopic procedures in gynaecological oncology are being conducted by pioneering experts in a few laparoscopy centres, and that gynaecological oncologists as a group are trying to define their position regarding the integrated role of laparoscopic surgery for oncology means.

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This study was carried out on behalf of the Surgical Subcommittee of the EORTC Gynecological Cancer Cooperative Group (GCCG).

Therefore, the EORTC Gynaecology Group sent a questionnaire to the active member institutes about the present role of laparoscopy in the clinical practice of gynaecological oncology in Europe. On 6 May 1994 a workshop was held in Turin, Italy, and the results of this European survey were presented. Furthermore, data and experiences of member institutions in oncology LS were discussed, and the European point of view regarding laparoscopy in gynaecological oncology was further defined.

Out of 69 institutions, 40 (58%) answered the questionnaire. The results of this survey have been divided into two parts:

PART 1: GENERAL OPINION ABOUT LS

The majority of the responding institutions (76%) believed that LS has a definite role in the treatment of gynaecological malignancies, while 21% had some doubts and 3% were against LS in gynaecological oncology at all. As far as the main indications were concerned, second-look laparoscopy for ovarian cancer and/or pelvic lymphadenectomy was considered feasible by 28% of the institutions. Ten per cent of the institutions considered LS feasible for every possible surgical procedure in gynaecological cancer. Twenty-three per cent of the institutions regarded second-look surgery a contraindication for LS, 21% of the centres considered pelvic lymphadenectomy not an advisable indication for LS. Each institution was asked to indicate on a five-point scale (1 = no role, 5 = very important role) the role of LS in different surgical procedures (Table 1). The analysis of the responses indicated a cautious recommendation of three of the four procedures. However, LS was considered to have no role or only little use for the performance of (radical) hysterectomy. The majority of the institutions suggested that LS is a necessary tool for every gynaecological oncologist, and that it is an essential technology for a modern oncology centre.

PART II: EXPERIENCE IN ONCOLOGY LS

Of the 40 responding institutions, 28 (70%) used LS. Twenty-three per cent of the institutions performed LS systematically, 54% in selected cases and 23% never in the treatment of gynaecological malignancies. Within the user institutions, an average of 15% (range 1–46%) of oncology surgery was performed by LS. As far as the indications were concerned, 27% of the user centres employed LS for second look in ovarian cancer, 13% for both second-look and lymphadenectomy, and 10% used LS for various oncological indications, e.g. second-look surgery, lymphadenectomy, staging work-up and radical surgery.

Within the 28 centres that used LS in oncology surgery, 14 (50%) performed lymphadenectomy by LS. Of these, 11 only performed removal of external iliac nodes, three also removed obdurator nodes and one performed para-aortic lymphadenectomy by LS. The average number of lymph nodes removed by LS was 10 (range 5–20) versus 25 (range 7–45) when the lymphadenectomy was performed by open surgery.

Independent of own experience, the majority of user institutions (18/28) believed that it is necessary to further develop the general application of LS in second-look for ovarian cancer and in lymphadenectomy. As far as staging for cervical or endometrial cancer and radical surgery is concerned, it was reported that LS should be reserved for selected situations only.

At the workshop, a length discussion on the advantages and disadvantages of potential applications for LS in gynaecological oncology took place. From this discussion, a number of conclusions could be made regarding the present European position and expectations, with respect to oncology laparoscopy in gynaecological practice:

(1) An established role for laparoscopy in the management of ovarian cysts is clear, provided that a number of prerequisites are met. The ultrasound characteristics of the cyst should be non-suspicious for malignancy. Vaginal echography is recommended. Postmenopausal women should be treated with laparotomy, and the aspiration of ovarian cysts should be discouraged because of the risk of slowly leaking tumour spill. It should, furthermore, be remembered that in case of a strong clinical suspicion of ovarian cancer, laparoscopy can be used to confirm the diagnosis histologically by laparoscopically directed biopsies. It is stressed, however, that, especially in the case of malignant ascites, this procedure may cause metastases in the troicart site.

(2) Second-look laparoscopy in patients with clinically complete remission after treatment for advanced ovarian cancer can detect residual disease in up to 50% of cases, thereby avoiding a laparotomy. However, the lack of effective salvage treatment regimens in ovarian cancer has greatly reduced the application of second-look surgery for ovarian cancer.

(3) Although it becomes increasingly clear that pelvic lymph node sampling by the laparoscope is technically feasible, a less radical resection can be done as compared to open surgery. As yet there is no consensus among the EORTC Gynaecology Group on the issue of pelvic lymphadenectomy in cervical cancer, and therefore, the role of laparoscopically performed pelvic lymph-node sampling cannot be defined at the present time.

(4) Laparoscopically assisted vaginal hysterectomy (LAVH) has proven its value in benign gynaecological disease. It is emphasised that in this procedure the ovaries and round ligaments are freed from above, and all the rest, including the uterine vessels, are clamped and ligated transvaginally using conventional vaginal hysterectomy techniques. Although the option of LAVH for the treatment of stage I endometrial cancer with favourable prognostic indices was

Table 1. Opinions on the role of laparoscopic surgery (LS) in performing various surgical procedures in gynaecological oncology

	Role of LS(%)				
Surgical procedures	No role	Little use	Worth using	Important	Very important
Second-look for ovarian cancer	12.5	35	30	17.5	5
Lymphadenectomy	20	20	40	15	5
Staging procedure	20	25	32.5	17.5	5
(Radical) hysterectomy	60	30	7.5	2.5	—

not very often mentioned in the EORTC survey, this application was considered as a significant further contribution to the treatment modalities of endometrial carcinoma at the workshop.

(5) It was concluded that LS is associated with a distinctly shorter hospitalisation. Despite this fact, laparoscopy is not invariably cheaper than open surgery due to the longer operating time and the higher costs of (disposable) instruments.

(6) Currently, the experience of laparoscopic procedures in gynaecological oncology is in the hands of relatively few laparoscopic pioneers and virtuosos. They have shown that very much is technically feasible in oncology laparoscopy. Now is the time to show the true value and real benefits of laparoscopy in controlled clinical trials. In order to conduct these trials, it is necessary to disseminate knowledge on LS among the practising gynaecological oncologists. This has still to be achieved.

CONCLUSION

In conclusion, the role of laparoscopy in gynaecological oncology is currently undefined. The main conclusion from the EORTC survey is that the actual experience and application of LS in gynaecological oncology is still limited among EORTC member institutions. Laparoscopy seems to have a distinct place for the management of ovarian cysts. It can prevent unnecessary laparotomies as a second-look procedure in patients with a clinically complete remission of advanced ovarian cancer. LAVH seems to be a promising new application for the treatment of early endometrial cancer with favourable features. Controlled clinical trials are needed to allow an accurate assessment of the clinical significance of oncology laparoscopy.

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EWOC-4 Conference Abstracts

Gene Therapy for Cancer

M. Gore

GENE THERAPY may be 'direct' or 'indirect'. Direct therapy alters a DNA sequence that is responsible for a malignant transformation or its maintenance, e.g. the ablation of an oncogene or the addition of an absent tumour suppressor gene. Indirect gene therapy involves inhibiting the growth of a tumour cell via an intermediate step, such as the insertion of a DNA sequence whose expression alters the host-tumour immune response, interrupts the pathways controlling tumour angiogenesis or results in the expression of a prodrug target (gene-directed enzyme prodrug therapy, G-DEPT). Strategies involving direct gene therapy target the tumour cell itself, indirect therapies can also involve targeting the tumour cell genome but may be directed at non-tumour host cells, e.g. lymphocytes or endothelial cells.

Physical methods of gene transfer include direct injection of DNA, either into a particular organ [1] or microinjection into specific cells [2], the use of high velocity microprojectiles [3] and electroporation during which small electric currents are passed through cell suspensions in the presence of the gene to be inserted [4]. Chemical methods of gene transfer use calcium phosphate precipitation [5], liposomes or lipofectin [6, 7] and carrier complexes with molecules such as polylysine [8] or DEAE-dextran bound to DNA [9]. Carrier complexes can be linked to specific cell surface receptor ligands e.g. monoclonal antibodies. The most efficient methods of gene delivery use viruses, mainly retroviruses, adenoviruses, adeno-associated viruses and herpes simplex virus.

Three types of gene therapy are currently being used in cancer: the first is the addition of suicide genes (G-DEPT) [10], the second, immunotherapy protocols where either target tumour or effector cells are modified in order to enhance or induce a host anti-tumour response [11–13] and thirdly, the insertion of the multidrug resistance gene, *MDR-1*, into bone marrow stem cells to allow increasing doses of chemotherapy to be delivered [14]. A fourth non-therapeutic intervention makes use of marker gene techniques [15].

The principle of G-DEPT involves the integration of a gene that encodes for a specific enzyme which converts an otherwise non-toxic prodrug into a toxic metabolite. Examples of this include the enzymes cytosine deaminase (5-fluorocytosine to 5-fluorouracil) [16] and herpes simplex virus thymidine kinase (phosphorylation of acyclovir or gangciclovir to their triphosphate forms) [17]. There is the problem of the efficiency of integration with G-DEPT, as not all cells will contain the gene encoding the suicide enzyme. Interestingly, it appears that a proportion of non-infected cells are also killed when the prodrug

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