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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Gene Therapy for Cancer

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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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is given and this is known as the 'bystander' effect [18]. There is animal evidence to suggest that this phenomenon is due to a host immune response. Immunotherapy protocols represent the majority of the currently approved gene therapy trials in cancer, and as a result mainly involve patients with renal cell carcinoma or melanoma. These studies can be divided into those that modify tumour cells and those that modify lymphocytes. The commonest approach is to modify cells to produce cytokines, either IL-2, IL-4 GMCSF, gamma interferon or TNF. The genes encoding for these cytokines are inserted into either autologous or allogenic tumour cells [19]. These protocols are best viewed as genetically-modified vaccine strategies. Other protocols use either peripheral blood or tumour infiltrating lymphocytes and these are similarly infected with cytokine genes [20, 21]. A small number of groups have developed a strategy based on the idea that by inserting the *MDR-1* gene into normal cells, increasing doses of chemotherapy can be administered with a resulting improvement in therapeutic index. Marker gene protocols give valuable information on the efficacy of high dose chemotherapy with autologous transplantation. Marker genes are inserted into bone marrow harvests prior to autologous transplantation allowing the source of any subsequent malignant cells that appear at relapse to be identified. The techniques involved can be used to examine whether or not 'purging' the harvest is valuable and can even compare two different methods of purging in the same patient.

In November 1989, the U.K. Government established the Committee on the Ethics of Gene Therapy under the Chairmanship of Sir Cecil Clothier [22]. It drew up ethical guidelines on the use of gene therapy, and its main recommendations were that somatic cell therapy should be allowed, but that genetic modification of germ line cells such as sperm, ovum or early embryos should not. In addition, they recommended that the Government set up a non-statutory advisory body known as the Gene Therapy Advisory Committee (GTAC) to oversee the conduct of gene therapy trials in the U.K. GTAC advises on the acceptability of all gene therapy proposals on human subjects examining the ethics, scientific merits and potential benefits and risks to the patient.

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