Lymph node staging in early-stage ovarian cancer

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Chapter 8

Valorisation addendum
Why is this thesis relevant?

Although clinical early-stage ovarian cancer and lymph node metastases have been studied for many years, still numerous questions both regarding the staging procedure as well as treatment are unsolved. In this thesis the incidence of lymph node metastasis in clinical early-stage ovarian cancer was reviewed, and in a large retrospective study the value of both the removal of lymph nodes as part of a surgical staging procedure and adjuvant chemotherapy was studied. Furthermore a new sentinel node procedure was tested in which the tracers were injected in the ovarian ligaments instead of in the ovary itself.

Relevance

Value of an adequate lymph node sampling as part of a surgical staging procedure

A lymphadenectomy is a radical procedure that is associated with morbidity, including nerve and vessel injury, increased blood loss, increased operating time, and the formation of lymphocysts and lymphedema. According to the International Federation of Gynaecology and Obstetrics (FIGO), ovarian cancer with lymph node metastases is classified as FIGO stage IIIA disease for which adjuvant chemotherapy is indicated. Our review on the incidence of lymph node metastases in early-stage ovarian cancer has shown that the overall incidence of lymph node metastases is 14%, which cannot be ignored. Only in case of a grade 1 mucinous ovarian tumour an adequate lymph node staging may be omitted.

Value of adjuvant chemotherapy in patients with early-stage invasive epithelial ovarian cancer

The role of adjuvant chemotherapy in adequately staged patients without lymph node metastases is still controversial. Some studies have indicated that, irrespective of the extensiveness of a staging procedure, adjuvant chemotherapy improves survival. Others have stated that adjuvant chemotherapy in these patients is only indicated in case of high risk factors such as FIGO stage IC and IIA and/or differentiation grade 3 and/or clear cell histology.

Our large retrospective study on the value of adjuvant chemotherapy has provided further evidence that, after an adequate staging procedure including at least 10 and preferably 20
or more lymph nodes, adjuvant chemotherapy is not indicated, even in patients with high risk factors.

**SN technique by injecting tracers into the ovarian ligaments**

Research on sentinel node technique in ovarian cancer is scarce. Only two studies, performed in patients with endometrial cancer, SNs were identified after injecting the tracers in the ovarian cortex. Injecting tracer in a tumour, especially one in the ovary can cause tumour spillage, and thereby metastasis. By injecting the tracers in the ovarian ligaments we have introduced a new technique for the detection of the sentinel node in ovarian cancer which appears to be promising.

Knowledge of the lymph drainage patterns of the ovary is essential to know where to look for positive lymph nodes during surgery. In the regions where lymph node metastases can be found, up to 200 or more lymph nodes are found. To remove them all would be an extensive procedure, leading to more morbidity among others increased blood loss and higher risk of lymphocysts and lymphedema.

Our study in which the lymphatic drainage pathways of the ovaries in three human foetal pelves immunohistochemically were studied provided further evidence that the ovarian ligaments are a good alternative site for injection of the tracers.

**Target groups**

The results of this thesis are interesting for gynaecologists, gynaecologic oncologists, medical oncologists, pathologists, nuclear medicine physicians, treatment developers and, most important, hopefully in the near future also for patients. When indeed the SN procedure in ovarian cancer appears to have a high accuracy as is the case for other tumours such as breast and vulvar cancer, more patients with clinical early-stage cancer will obtain an adequate staging procedure without the accompanying morbidity related to a complete pelvic and para-aortal lymphadenectomy.

**Activities and Innovation**

By injecting the tracers in the ovarian ligaments we have introduced a new technique for the detection of the sentinel node in ovarian cancer. In our feasibility study we found a
high detection rate of sentinel nodes and no side effects were seen due to the procedure. Also the procedure appeared to be safe for the involved health care workers. Our results have been published in scientific research journals. We have had the opportunity to discuss our findings nationally and internationally to gain more attention for this important topic. We still need to further explore this new technique and this leads to more research.

**Schedule and implementation**

The results of the feasibility study on identifying SNs in patients with ovarian cancer are promising, but needs additional research. Remaining questions which need to be answered are:

- **Is a SN procedure through injection of the tracers in the ovarian ligaments still feasible immediately after a salpingo-oohorectomy is performed?**
  
  In our feasibility study in which tracers were injected into the ovarian ligaments to identify possible sentinel nodes, the injection occurred before the adnex was resected for frozen section. However, this means that in a significant number of patients the injection of tracers is unnecessary when the result of frozen section indicates a benign of borderline lesion for which no lymph node resection is necessary.

- **Is a SN procedure through injection of the tracers in the ovarian ligaments still feasible in patients in whom the malignant ovarian tumour has already been resected?** This concerns patients in whom previously the ovarian tumour has been resected because it was not suspected to be malignant.

- **Is the fact that, in our study, the majority of the sentinel nodes identified by the gamma probe did not show blue colorization is caused by a long time-interval between injection and retroperitoneal exploration?**

- **Can the use of a mobile gamma camera during the surgical procedure enhance intraoperative detection of sentinel nodes?**

- **Can multimodality radioactive and fluorescence guidance enhances intraoperative detection of sentinel nodes?**

Some of these questions will be answered in the SONAR 2 study that recently is initiated in the Maastricht University Medical Centre+, in cooperation with two other gynaecologic oncology centres (Radboud University Medical Centre and Antoni van Leeuwenhoek Hospital Amsterdam).
When these questions are answered, hopefully resulting in a more profound technique, a (inter)national prospective multi-centre trial could be done to determine the diagnostic accuracy of the sentinel lymph node procedure in patients with ovarian cancer. In this study, after removal of the first sentinel lymph node, subsequently an adequate lymph node sampling (at least 10, and preferably 20 or more lymph nodes from the pelvic and para-aortal regions) is performed to establish the incidence of false negative lymph nodes and the incidence of unrecognized sentinel nodes. This gives MUMC+ the opportunity to become the leading centre for research concerning the sentinel node procedure in ovarian cancer.

Hopefully, when the technique is proven to be effective, it will become part of the daily practice in treatment of early-stage ovarian cancer worldwide.