

My paper selection is 'Paradigm shift in the management of gynaecological cancers' by Sap and Van Trappen. This paper is of interest because it summarises the advances in the management of gynaecological cancers. More importantly it emphasises a multidisciplinary approach to these tumours, which not only improves the outcome but also increases the diagnostic accuracy and decreases morbidity.

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PARADIGM SHIFT IN THE MANAGEMENT OF GYNAECOLOGICAL CANCERS

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ABSTRACT

In this review we highlight novel aspects of diagnostic imaging in gynaecological cancers, the paradigm shift in the surgical management of certain female pelvic cancers, as well as potential new molecular targeted therapies. In the last decade, ultra-radical surgery has been shown to increase survival in advanced ovarian cancer (OVC) when extended surgical procedures are included during primary cytoreductive surgery or at interval debulking procedures after neoadjuvant chemotherapy. In cervical cancer (CVC) and endometrial cancer (EMC) endoscopic (laparoscopic or robotic) operations have been shown to significantly reduce the morbidity without altering the cancer-related survival. Although the sentinel lymph node concept is already established in early-stage vulvar cancer, its diagnostic accuracy in EMC and CVC is still under debate. Novel molecular targeted therapies including blocking agents against new blood vessel formation (anti-angiogenesis) and polyadenosine diphosphate ribose polymerase inhibitors have been shown to prolong the progression-free survival in advanced OVC. Other molecular therapies, single or combined, are under investigation in OVC and EMC.

Keywords: Ovarian cancer, endometrial cancer, cervical cancer, positron emission tomography (PET), magnetic resonance imaging (MRI), ultra-radical surgery, robot, sentinel lymph node, molecular therapy.

INTRODUCTION

Pelvic gynaecological cancers (GYC) include cancer of the vulva, vagina, cervix, uterine corpus, fallopian tubes, and ovaries. The primary treatment depends mainly on the tumour type (e.g. carcinoma versus sarcoma) and stage of disease, but usually involves surgery in early-stage disease and surgery combined with (neo) adjuvant chemotherapy and/or radiotherapy in high-risk early-stage or advanced

stage of disease. Worldwide, cervical cancer (CVC) is the fourth most common cancer in women, with an estimated 528,000 new cases in 2012. The majority of new CVC cases and CVC mortality occurs in the developing world.¹ In developed countries, the most commonly diagnosed GYC is uterine cancer with 320,000 new cases in 2012 worldwide, of which 52.5% were in the more developed world. Endometrial cancer (EMC) has an incidence rate of 26.5 per 100,000 women per

year in the United States. However, ovarian cancer (OVC) has the highest mortality rate and claims more lives than the other gynaecological malignancies combined: 7.8 per 100,000 in 2009 in the United States.²

New diagnostic imaging modalities such as 18F-fluorodeoxyglucose positron emission tomography (PET)/computed tomography (CT) and diffusion-weighted or dynamic contrast-enhanced magnetic resonance imaging (DWI-MRI or DCE-MRI) are focusing more on potential local tumour activity besides structural changes.³⁻⁵ Molecular imaging, mainly PET and MRI, plays an important role in the management of gynaecological malignancies, and has an impact in different clinical settings.

The surgical management of pelvic GYC has undergone a paradigm shift, especially in the past decade. It has evolved from open surgery to less invasive endoscopic procedures (i.e. laparoscopic or robotic) for EMC and CVC on one hand, and to more ultra-radical surgery (URS), especially in the upper abdomen, for the treatment of advanced OVC on the other hand. In addition, the concept of the sentinel lymph node (SLN) is now being explored in early-stage EMC and CVC, despite being already established in vulvar cancer (VUC). Molecular therapies, often targeting/blocking growth factor receptors on tumour cells or vascular endothelial cells, have recently been introduced in the management of GYCs, and this has opened up new horizons for individualised treatment. In this review we discuss the current and potential future novel strategies in the management of different pelvic female cancers.

MATERIALS AND METHODS

A search of the PubMed and MEDLINE databases for articles published before January 2015 was performed. Only English language articles were considered. Search terms included 'cervical cancer', 'endometrial cancer', 'uterine cancer', 'ovarian cancer', 'fallopian tube cancer', and 'vulvar cancer', in association with 'surgery', 'laparoscopic surgery', 'robotic surgery', 'ultra-radical surgery', 'sentinel lymph node', 'staging', 'molecular imaging', 'PET', 'CT', 'PET/CT', 'PET/MRI', 'MRI', or 'molecular therapies'. With the selection criteria used 78,926 papers were found. For this review, recent papers were selected in case they reported results from prospective (randomised) trials, (observational) cohort studies, comparative studies, case-

matched controlled studies, systematic reviews, or meta-analyses.

NEW CANCER IMAGING MODALITIES

MRI and PET, often combined with computed tomography (PET/CT), have become increasingly important in the management of gynaecologic malignancies. MRI has become the mainstay of imaging modalities in staging and follow-up of EMC and CVC.⁶ In EMC, MRI is used for assessing the depth of myometrial invasion and cervical extension, hence selecting patients for lymphadenectomy. In CVC, MRI is used in initial staging, assessing local tumour infiltration in surrounding tissues, monitoring response to primary (chemo) radiotherapy, and detecting local recurrence. It is also important in determining the feasibility of fertility-preserving surgery, i.e. radical amputation (radical trachelectomy), or conisation of the cervix in young women, by assessing proximal extension of the tumour. PET/CT appears to be valuable for initial staging in CVC and for detection of recurrent disease. In OVC, PET/CT can be useful in detecting recurrent disease in the setting of a rising CA-125 level without remarkable anatomical imaging findings.³

In a recent study, whole-body DWI-MRI has been shown to help assess operability of OVC, for example it improves detection of mesenteric and serosal metastatic spread when compared with CT.⁷ The focus of imaging in gynaecological malignancies has shifted recently from visualising morphological/structural changes to detecting local tumour activity. PET/CT and new applications of MRI have been shown to be especially useful in providing this kind of functional information. PET/MRI has been shown to offer higher diagnostic confidence in the discrimination of benign and malignant lesions in gynaecological malignancies compared with PET/CT.⁸ In another study PET/MRI correctly identified 98.9% of malignant lesions, whereas MRI alone correctly identified 88.8% of malignant lesions.⁹ Considering the reduced radiation dose and superior lesion discrimination, PET/MRI may replace PET/CT in the future. Another MRI application is the DCE-MRI, which makes use of intravenous gadolinium-based contrast in providing information on angiogenesis. Especially in CVC, it may be useful in detecting small tumours and may also help distinguish between recurrent tumours and radiation fibrosis.¹⁰

ULTRA-RADICAL SURGERY FOR ADVANCED OVARIAN CANCER

Approximately 70% of OVC patients have advanced-stage disease. For several decades the inverse relationship between residual tumour after debulking surgery and overall survival (OS) has been the cornerstone of OVC treatment. Residual disease after primary debulking surgery (PDS) has been shown to be the single most important prognostic factor in advanced OVC. Hence, optimal cytoreductive surgery (CRS), combined with platinum-based chemotherapy, i.e. carboplatin/paclitaxel, remains the standard of care (SoC).

Primary URS in advanced OVC, as advocated by Chi et al.,¹¹ includes extensive upper abdominal surgery, such as diaphragm peritonectomy, splenectomy, distal pancreatectomy, partial liver resection, cholecystectomy, and resection of tumour from the porta hepatis when necessary.^{12,13} Their study showed an increase in 5-year OS from 34-47% when diaphragmatic surgery was included in the CRS. This effect has also been shown by Aletti et al.¹⁴ By aggressive intestinal surgery optimal cytoreduction can be achieved in more than 70% of cases.¹⁵ Cai et al.¹⁶ showed that in patients where bowel resection was considered, 67% had optimal cytoreduction with a median survival of 50 months, compared to 45% optimal debulking in patients where no bowel resection was performed with a median survival of 44 months. However, URS comes with a significant complication rate and post-operative morbidity, such as digestive fistula, lymphocysts, and septic and pulmonary complications.^{13,17} Wright et al.¹⁸ showed that the number of extended radical procedures (e.g. diaphragmatic surgery, bowel resection) was directly related to the percentage of complications, with 20%, 34%, and 44% complications when zero, one or two radical procedures were performed, respectively.

Another approach to achieve optimal cytoreduction in advanced-stage OVC is to perform an interval debulking surgery (IDS) after neoadjuvant chemotherapy (NAC). This approach appears to improve short-term morbidity, while retaining a similar survival rate (SR).¹⁹ Despite recent randomised controlled trials addressing this issue and demonstrating non-inferiority of the NAC-IDS concept, the debate on PDS versus NAC-IDS continues.²⁰ Significant efforts have been made to further define subgroups of patients who would benefit most from NAC, such as patients with

small volume disease widespread on peritoneal surfaces and bowel serosa, but no consensus has been reached. A possible role for an explorative laparoscopy to help triage patients towards PDS or NAC has been demonstrated.^{21,22}

LAPAROSCOPIC AND ROBOTIC SURGERY IN ENDOMETRIAL AND CERVICAL CANCER

Since the introduction of laparoscopic surgery in benign gynaecology in the 1980s and in gynaecological oncology in the 1990s, two large prospective randomised trials (the LACE001 trial and the total laparoscopic hysterectomy [TLH] study) showed in 2010 less morbidity (less blood loss, less pain, shorter hospital stay, and faster recovery) for TLH as compared to total abdominal hysterectomy (TAH) in early-stage EMC.^{23,24} The Gynecologic Oncology Group (GOG) LAP2 study in EMC showed an almost identical 5-year OS in both arms (TLH and TAH) at 89.8%.²⁵ In addition, laparoscopic procedures in CVC, such as laparoscopically assisted radical (vaginal) hysterectomy, have been shown to be feasible and safe with regards to mortality combined with low morbidity.²⁶

Since FDA approval in 2005 for the use of the Da Vinci Robotic surgical system there has been a paradigm shift towards more minimally invasive surgery, not previously achieved with traditional laparoscopy. This resulted in more than 50% of endometrial staging procedures being performed by robotic-assisted surgery in 2010 in the United States.²⁷ This may be due to its shorter learning curve for performing complex gynaecological oncological procedures compared to laparoscopy. There might also be particular advantages of robotic surgery over traditional laparoscopy in obese patients.²⁸ Technical advantages for the surgeon are the improved three-dimensional stereoscopic vision, the wristed instruments, and improved surgical precision with tremor-cancelling software. The main limitation of robotic-assisted procedures is the higher cost; however, this may decrease with increased utilisation.

Several research groups have reported outcomes (e.g. complications, survival) of robotic-assisted hysterectomy or radical hysterectomy with pelvic lymph node dissection in EMC and CVC, respectively, proving the feasibility and safety in gynaecological oncology.²⁹⁻³⁵ Compared to

laparoscopic procedures, the robotic approach is associated with less blood loss and shorter hospital stay.³⁶ There is no significant difference in the yield of lymph nodes and the percentage of peri or post-operative complications for robotic-assisted versus laparoscopic procedures (see Table 1). Several Phase III trials are ongoing, such as the LACC001 trial, which compares total laparoscopic radical hysterectomy or total robotic radical hysterectomy with total abdominal radical hysterectomy for the treatment of early-stage CVC.

SENTINEL LYMPH NODES IN GYNAECOLOGICAL CANCERS

The SLN concept was introduced by Giuliano et al.³⁷ in 1994 in breast cancer (BrC) and since the 1990s it has become the SoC for early-stage BrC and malignant melanoma, resulting in a significant decrease in morbidity whilst retaining a similar SR.³⁸ In VUC, the SLN concept has been widely accepted as the SoC for unifocal, unilateral squamous cell cancer lesions of less than 4 cm, since the published data of the multicentre observational study by Van der Zee et al.^{39,40} They showed a low groin recurrence rate of 2.3% and

an excellent disease-specific SR of 97% at 3 years in sentinel node-negative patients, combined with a decreased short and long-term morbidity (less wound breakdown, cellulitis, recurrent erysipelas, and lymphoedema of the legs) compared to inguinofemoral lymphadenectomy.

Recent trials on SLN biopsy in EMC showed a large range of detection and false negative rates, but also used different SLN techniques: injectant (isosulfan blue, radioisotope, indocyanine green), injection site (uterine subserosa, cervix, or hysteroscopic injection into the endometrium) and pathologic technique are all of importance. To date, there is no standardised method for SLN biopsy in EMC. A recent prospective multicentre study⁴¹ investigated the detection rate and diagnostic accuracy of the SLN by cervical dual injection (with technetium and patent blue) in early-stage EMC. They included 133 patients from 9 centres. They found a sensitivity of 84% and negative predictive value (NPV) of 97% for the SLN. A thorough review by Levinson and Escobar⁴² reported detection rates range from 62-100%, with false negative rates between 0-50% and NPVs from 95-100%. It is clear that larger trials are needed to more accurately determine the efficacy of the SLN concept in EMC.

Table 1: Overview of selected papers on robotic surgery in endometrial cancer (EMC) and cervical cancer (CVC).

Author	Year	Procedure: (radical) hysterectomy + pelvic LNN	Total number of patients	Operating time (min)	Blood loss (ml)	LNN	Hospital stay (days)	Intra-operative complications (%)	Post-operative complications (%)
Lowe et al. ²⁹	2009	Robotic (EMC)	405	170.5	87.5	15.5	1.8	3.5	14.6
Lim et al. ³⁰	2011	Robotic vs. LSK (EMC)	122 122	147.5 186.8	81.1 207.5	19.2 24.7	1.5 3.2		
Cardenas-Goicoechea et al. ³¹	2010	Robotic vs. LSK (EMC)	102 173	237 178	109 187	22 23	1.88 2.31	2 6	15 33
Lowe et al. ³⁴	2009	Robotic (CVC)	42	215	50	25	1	4.8	12
Chong et al. ³²	2013	Robotic vs. LSK (CVC)	50 50	230 211	55 202	25 23.1		0 8	
Hoogendam et al. ³³	2014	Robotic (CVC)	100	319	185	24	4		
Reynisson et al. ³⁵	2013	Robotic vs. open (EMC+CVC)	180 51	185-314 233	100 700		2.4-5.5 7.3	2 6	15 33

LNN: average number of prelevated lymph nodes per surgical procedure; vs.: versus.

Deep injection into the cervix has a clear technical advantage compared to injection into the uterine subserosa or hysteroscopic injection into the endometrium, as it is the easiest site to reach pre-operatively. Furthermore, this injection site has been proven to reach the proper areas of drainage.⁴³

A recent systematic review and meta-analysis⁴⁴ assessed the accuracy of the SLN procedure in patients with early-stage CVC. The authors identified 49 eligible studies, which included 2,476 SLN procedures. The overall detection rate was 93% and pooled sensitivity was 88%. It was concluded that the SLN procedure performed well diagnostically in patients with early-stage CVC. However, larger prospective trials are needed to elucidate its value in the standard surgical management of early-stage CVC. Finally, the importance of ultra-staging and the use of immunohistochemistry in addition to standard haematoxylin and eosin staining has proven to be vital in the validity of the SLN concept.^{42,45}

MOLECULAR TARGETED THERAPIES

Since the 1990s, the standard (neo) adjuvant chemotherapeutic treatment in most OVCs has been carboplatin and paclitaxel. More recently, the addition of molecular targeted agents such as molecules that block new vessel formation (anti-angiogenesis) has demonstrated a prolonged progression-free survival (PFS) in Stage 3 OVC. In addition, the value of polyadenosine diphosphate ribose polymerase (PARP) inhibitors as second or third-line therapy has been shown in the treatment of recurrent OVC. Bevacizumab, the anti-VEGF (vascular endothelial growth factor) monoclonal antibody, has been shown to improve PFS in newly diagnosed OVC, and in both platinum-sensitive and platinum-resistant recurrent OVC in several trials, most importantly the ICON7, GOG218, OCEANS, and AURELIA trials.⁴⁶⁻⁴⁹ In the ICON7 trial, including 1,528 patients with newly diagnosed OVC, the benefits (PFS and OS) of bevacizumab were greater in those patients at high risk for progression of disease. In the OCEANS trial, including 484 patients with platinum-sensitive recurrent OVC, the PFS was in favour of the bevacizumab group: 12.4 months versus 8.4 months. In the AURELIA trial, including 361 patients with platinum-resistant recurrent OVC, the PFS was 6.7 months in the bevacizumab arm versus 3.4 months in the placebo arm.

More recently, oral alternatives (pazopanib, nintedanib, cediranib) to the intravenous administered bevacizumab have been studied in trial settings, showing often concordant findings with the use of bevacizumab. Prolonged PFS was seen when for example pazopanib was given as maintenance treatment, nintedanib concomitant to chemotherapy and further as maintenance treatment, and cediranib as maintenance treatment.^{50,51}

Olaparib is a potent oral PARP inhibitor that has shown antitumour activity in patients with high-grade serous OVC. The PARP enzyme plays an essential role in repair of single-stranded DNA breaks. In tumours with homologous recombination deficiency (HRD), PARP inhibition leads to the formation of double stranded DNA breaks that cannot be accurately repaired, and thus to cell death. HRD can be found in approximately 50% of serous OVCs. This is not only due to a germline or somatic mutation of *BRCA1* or *BRCA2*, but also due to epigenetic silencing of the *BRCA* genes or to the mutation of other genes involved in HRD.

In a randomised controlled Phase II study by Ledermann et al.,⁵² olaparib has been shown to improve PFS in patients with platinum-sensitive relapsed high-grade serous OVC (PFS in the overall study group: 8.4 versus 4.8 months; PFS in the subgroup of *BRCA*-mutated patients: 11.2 versus 4.3 months). However, at the interim analysis this did not translate into an OS benefit. Currently, there are four ongoing randomised placebo-controlled trials of maintenance therapy with a PARP inhibitor. The latest trials in OVC focus on detecting subgroups that are especially sensitive to a certain form of targeted therapy (e.g. the SOLO trials, evaluating olaparib in *BRCA*-positive ovarian cancer) or combinations of targeted therapy that are possibly more potent (e.g. combining olaparib and cediranib in OVC).⁵³

The chemotherapy of choice in advanced EMC is the combination of carboplatin and paclitaxel, as in OVC.^{54,55} However, OS in patients with advanced EMC is poor. Hence, better therapy is needed and targeted molecular therapies are emerging as possible treatment candidates. These include molecules that target VEGF (bevacizumab), mammalian target of rapamycin (mTOR; temsirolimus and everolimus), tyrosine kinase receptors (sorafenib), human epidermal growth factor (EGF) receptors (erlotinib), and human EGF Receptor-2 (HER-2; trastuzumab).⁵⁶ With these

targeted therapies partial response was seen in up to 12.5% of cases and stable disease in up to 48% of cases, lasting for at least 4 months. Patients with metastatic and/or inoperable locally advanced recurrent CVC who have been treated before with chemoradiotherapy constitute a high-risk population with a difficult therapeutic challenge. For these patients, the FDA has recently (August 2014) approved the anti-angiogenesis drug bevacizumab.⁵⁷

CONCLUSION

Imaging in pelvic GYCs has evolved from standard CT scan and MRI to the combination of PET with CT and whole-body DWI or DCE-MRI, focusing on potential local tumour activity besides structural changes. Given the superior lesion discrimination of MRI compared to CT, whole-body DWI-MRI combined with PET may replace PET/CT in the future. URS with extended surgical procedures such as diaphragmatic stripping and bowel resection is associated with longer PFS and OS in advanced OVC. Hence, randomised trials

are needed to consolidate this. Laparoscopic procedures in CVC and EMC have been shown to be safe in terms of survival, with similar SRs as in open surgery, but with a decreased morbidity for the patients. Robotic surgery is recently emerging in the management of early-stage EMC and CVC with less blood loss and shorter hospital stay. The concept of the SLN procedure performed diagnostically well in patients with early-stage CVC and EMC in recent trials, but larger prospective studies are needed.

Molecular targeted therapies such as blocking new blood vessel formation (anti-angiogenesis) and PARP inhibitors have been shown to increase PFS in advanced/relapsed OVC. Other targeted therapies such as mTOR or tyrosine kinase inhibitors have been shown to induce stable disease for several months in advanced/relapsed EMC. Recently, the FDA and European Medicines Agency have approved the anti-angiogenesis drug bevacizumab for women with advanced CVC. Results from single or combined molecular targeted therapies in trial settings in GYCs are awaited.

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