Imaging in recurrent ovarian cancer

G Dreyer, G Lindeque
Gynaecologic Oncology Unit, Department of Obstetrics & Gynaecology, University of Pretoria, Pretoria, South Africa

Introduction

Epithelial ovarian cancer is mostly a disease of the peritoneal surfaces of the abdomen. The disease often causes disseminated small volume implants with a consistency similar to that of normal tissue rather than a large identifiable tumour mass, usually with the exception of the pelvic ovarian tumour. Imaging for ovarian cancer is therefore problematic and especially peritoneal disease, nodal deposits and omental disease are difficult to demonstrate accurately.[1]

The accuracy of different imaging modalities to predict operability or tumour volume in primary disease have been studied extensively and found generally to lack accuracy.[2] In this review the focus will be on the role of these radiological modalities in recurrent ovarian cancer. Imaging after previous surgery, chemotherapy and intra-peritoneal chemotherapy has the same lack of sensitivity.[1] In addition false positive results due to adhesions, tumour necrosis and fluid pockets are demonstrated.

In the light of the above and remembering the cost of these tests, it is important to consider the aims of imaging in recurrent ovarian cancer, the actions that may follow and the ideal tests to be used in the different clinical situations. The discussion thus involves the philosophy of the follow-up of patients with previous late stage ovarian cancer.

The diagnosis of recurrent ovarian cancer

In any evaluation of the use of diagnostic modalities in recurrent cancer, the possible therapeutic options and the impact of these therapies on quality of life and survival remains important questions that needs to be discussed. Epithelial ovarian cancer is the most lethal of all gynecological malignancies and is recurrent in nature.[3] Around 75% of patients present with stage III and IV disease and the majority of these women will experience multiple recurrences and eventually succumb to the disease. Improved surgical techniques and ever increasing chemotherapeutic options have not changed this outcome.[3,4]

Late stage and recurrent ovarian cancer is now seen as a very serious and life-threatening chronic ailment with the management focusing on improved quality of life.[5] The ideal follow-up of these patients have not been established and most patients are currently followed both clinically and biochemically, while many will also have routine imaging tests scheduled aimed at earlier diagnosis of recurrent disease.

Whether initial follow up is done clinically or by biochemical testing and then followed by reflex diagnostic testing by radiology and/or biochemistry, probably has no influence on survival and a relatively small influence on timing of treatments.[6] In the majority of patients disease will recur biochemically before clinical recurrence. This type of follow-up decreases 'disease-free' and treatment-free intervals, while it enables earlier initiation of second and further lines of therapy.[7] It also creates a therapeutic challenge and demonstrates the dilemma caused by sensitive diagnostic tests. Unfortunately earlier diagnosis and earlier initiation of therapy for recurrent disease has never been demonstrated to improve overall outcome.[8]

Routine advanced imaging in the absence of both clinical and biochemical recurrence increases the costs of follow-up without demonstrated survival benefit. However, when imaging is done after the clinical suspicion of recurrent disease, the sensitivity of clinical follow-up is shown to be much improved. In women previously treated for epithelial ovarian cancer elevated or rising levels of Ca 125 suggest recurrence with reported specificity of between 93 and 100%.[6,7] Even advanced imaging techniques will often fail to demonstrate disease after this finding and thus cannot be used to confirm biochemical disease recurrence.

Correspondence:
Prof Greta Dreyer
email: Greta.dreyer@up.ac.za
Prof Gerhard Lindeque
email: Gerhard.Lindeque@up.ac.za

The aims of imaging in recurrent ovarian cancer

Sophisticated radiologic tests in women with clinical and/or biochemical recurrence aims to identify the site, size, nature and number of recurrent tumour deposits. Imaging has a role in decision making regarding trigger points for the initiation of chemotherapy and in the evaluation of chemo-response.[9] It also enables consideration of appropriateness and feasibility of secondary surgical removal[10] or even targeted radiation therapy.[11]

Imaging is used in relation to ovarian cancer in several roles: screening, diagnosis, detection of residual disease and detection of recurrent disease.

The imaging tests available are ultrasound, MRI, CT and PET/CT, all with various enhancer or contrast variations. This article focuses on detection and assessment of recurrent disease.

The context is that in all patients treated for ovarian cancer a regular screening protocol should be followed to detect asymptomatic recurrence. Such recurrence can be nodal, intraperitoneal or in distant organs.

Surgery for recurrent ovarian cancer

Strict criteria exist for secondary surgical removal of recurrent ovarian cancer.[12] Surgery is most beneficial and sensible in patients who have a better predicted prognosis (those with later recurrences and platinum sensitive tumours), better performance status and when recurrence is limited to one or at most two sites. For these patients surgery has been reported safe and achievable with minimal complications. Disease should not be associated with multiple peritoneal deposits and ascites.[13,14] Isolated pelvic and nodal recurrences are the easiest to remove successfully.

Patient selection is thus of utmost importance to avoid compromising quality of life. The most important and difficult decision is whether surgical resection (complete secondary cytoreduction) is feasible and potentially beneficial for the patient.[13,15,16] Expert pre-operative imaging will help to prevent unnecessary surgical exploration and surgery done at inappropriate levels of expertise and care. Better planning, patient information and more appropriate discussion before surgery will also result from improved pre-operative diagnosis.

Imaging modalities in recurrent ovarian cancer

Transvaginal ultrasound has a major role to play in the follow-up of patients treated for ovarian cancer as it has a high probability to detect pelvic cystic lesions and low volume ascites. It is commonly used in conjunction with clinical assessment and should be used at every follow-up visit. The limitations are that the test is really confined to the pelvis and that its ability to detect solid lesions is limited.

When MRI (magnetic resonance imaging) became available it was thought that this is the best test to use on a regular basis to detect asymptomatic disease in the entire body. This is commonly used in conjunction with CA125 determinations. Both tests have however been shown to have serious limitations. In the case of MRI the detection rate of later surgically proved recurrent ovarian cancer was low and only with enhancements could comparative results to other techniques be obtained.

CT (computerized tomography) scanning has taken centre stage for imaging tests to detect asymptomatic ovarian cancer recurrence. It has been demonstrated to be accurate and can detect solid small lesions, nodal lesions as well as lesions in distant organs. This has become the imaging test of choice to use on a regular (6-12 monthly) basis in these patients.

MRI may probably be slightly superior to CT in demonstrating the extent of soft tissue tumours and tissue planes, but CT more accurately demonstrates enlarged lymph nodes. Neither of these modalities can differentiate large malignant from non-malignant nodes and neither will show small nodal disease with accuracy.

With the availability of PET/CT the next step was to compare PET/CT to CT for accuracy, diagnostic ability and diagnoser (radiologist) consistency. Although reports are still scanty there is common cause that PET/CT scanning is as accurate or better than CT scanning with less interobserver variation.[17,18] The accuracy relates to finding proven recurrent disease after exploration.

PET/CT utilizes radiopharmaceuticals labeled with isotope, usually 2-[^{18}F]-flouro-2-deoxy-D-glucose, or FDG. This is a glucose analogue, which metabolite, FDG-6-phosphate, remains trapped within the cells. Cancer cells display an increased level of metabolism due to decreased levels of glucose phosphatase and increased glycolysis.

Many studies of the role of FDG PET have been performed, but most of them were limited by small numbers and the use of a PET scanner alone. Recent studies with PET/CT hybrid cameras demonstrated more accurate detection and localization of lesions.[19,20]

The main advantage of PET/CT scanning is that this modality combines the demonstration of structural anatomy with the measurement of increased metabolic activity. This combination is more accurate than structural imaging alone to establish a specific diagnosis and can benefit the patient in specific clinical situations. PET/CT is an appropriate imaging modality in selected patients with biochemically recurrent ovarian cancer when other modalities fail to demonstrate tumour and surgical management is an option. This combination has the ability to differentiate large malignant nodes from non-malignant disease. It is probably more sensitive for small retroperitoneal foci of disease including small volume nodal disease than the alternative tests.[20,21]

False positive results in this clinical scenario are scarce and reasons include other reasons for increased metabolic activity like infections and abscess formation. While PET/CT is often used to determine whether nodes demonstrated on other forms of imaging represent malignancy or not, reactive nodes due to non-malignant disease may show increased metabolic activity and lead to a false-positive test.[21,22]

PET/CT is not widely available and is very expensive. This test should be used selectively and the accumulation and repetition of advanced diagnostic imaging tests for individual patients should be prevented as far as possible.

Good practice

An inescapable variant is the cost of these tests. Many areas in the world function without easy availability of CT scanning let alone PET/CT. The cost of regular imaging is a factor to be taken into account as patients in the private and public sector alike may struggle to afford such tests.

Therefore a recommendation should be made for current practice:

- Patients treated for ovarian cancer should be followed regularly. The schema should consist of:
- Clinical assessment (symptoms and signs) with transvaginal ultrasound every 3-4 months
- Biochemical assessment of tumour markers, usually Ca125, at regular intervals
- Whole body imaging in case of asymptomatic patients: CT scanning annually or when recurrence is detected clinically or biochemically
- PET/CT scanning should be used if available and preferably in cases where the CT scanning in somewhat equivocal.

Finally it should be stated that the objective of searching for asymptomatic recurrence is to afford further treatment earlier rather than later. This is a shift in paradigm in managing recurrent ovarian cancer. It was previously held that once a patient recurs after treatment the only options were to offer (lesser) chemotherapeutic agents. Many patients will however benefit from second surgical attempts and multimodality treatment. To wait until a recurrence is symptomatic, large and multicentric does not serve the case of the patient. Effort and enthusiasm should be put into detecting recurrent disease as early as possible, to assess the scope of such recurrence, and to utilise the multidisciplinary team to work out treatment strategies for these patients.

It is common knowledge amongst patients and practitioners that the majority of patients treated for ovarian cancer will experience a recurrence. The patients live every day waiting for such recurrence to arrive. It would seem that equally serious vigilance on the part of the practitioner will be regarded as beneficence and the correct practice to follow.

Conclusion

The challenge facing us is to choose the best method per individual patient, always asking how the result will or can influence treatment and benefit the patient. Imaging should never substitute clinical evaluation or judgment and must not be done purely as part of defensive medicine. Imaging should also not be ordered to postpone difficult decisions or merely to act as a documentation of what is already known.

In low resource settings, including some tertiary hospitals, imaging is often under-utilized due to long waiting periods. This poor pre-operative diagnostic accuracy can lead to harmful interventions.

References

1. *Jacquet P, Jelinek JS, Stevens MA et al. Evaluation of Computed Tomography in patients with intraperitoneal carcinomatosis. Cancer 1993; 72: 1631-1636.*
2. *Revathy I. Imaging in gynaecologic malignancy. Sem Roentgenol 2004; 39(3): 428-438.*
3. *Ozols RF. Future directions in the treatment of ovarian cancer. Semin Oncol 2002: 29 (supp 1): 32-41.*
4. *Markman M, Bookman MA. Second-line treatment of ovarian cancer. Oncologist 2000; 5(1):26-35.*
5. *Armstrong DK. Relapsed ovarian cancer: challenges and management strategies for a chronic disease. The Oncologist 2002; 7 (supp 5) :20-28.*
6. *Vaidya AP, Curtin JP. The follow- up of ovarian cancer. Sem Oncol 2003; 30: 401-412.*
7. *Perkins GL, Slater ED, Sanders GK. Tumor markers. Am Fam Phys 2003; 68(6): 1075-1082.*
8. *Spriggs D. Optimal sequencing in treatment of recurrent ovarian cancer. Gynecol Oncol 2003; 90: 539-544.*
9. *Hauspy J, Covens A. Cytoreductive surgery for recurrent ovarian cancer. (Review) Curr Opin Obstet Gynecol 2007; 19(1):15-21.*
10. *Pfisterer J, Harter P, Canzler U, et al. The role of surgery in recurrent ovarian cancer. Int J Gynecol Cancer 2005; 15(S 3):195-198.*
11. *Dreyer G, Backer F. The role of radiation therapy in epithelial ovarian cancer. O & G Forum 2003:6-10.*
12. *Harter P, Du Bois A, Hahmann M, et al. Surgery in recurrent ovarian cancer : The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR Trial. Am J Surg Oncol 2006 ; 13(12) :1702-1710.*
13. *Eisenkop SM, Friedman RL, Spirtos NM. Role of cytoreductive surgery in treatment of patients with recurrent epithelial ovarian carcinoma. Cancer 2000; 88: 144-153.*
14. *Munkarah A, Levenback C, Wolf JK et al. Secondary cytoreductive surgery for localized intra-abdominal recurrences in epithelial ovarian cancer. Gynecol Oncol 2001; 81:237-243.*
15. *Tay EH, Grant PT, Gebski V et al. Secondary cytoreductive surgery for recurrent epithelial ovarian cancer. Obstet Gynaecol 2002; 99(6): 1008-1013.*
16. *Rose PG. Surgery for recurrent disease. Semin Oncol 2000; 27(supp 7): 17-23.*
17. *Sebastian S, Lee SI, Horowitz NS et al. PET/CT vs. CT alone in ovarian cancer recurrence. Abdom Imaning 2008: 33(1):112-8.*
18. *Javadi M. Shruti A, Bristow R, Wahl R. FDG-PET.CT in assessing ovarian cancer recurrence and patient outcome: Comparison to CA 125. J Nucl Med 2009: 50(suppl 2): 174.*
19. *Karlan BT, Hawkins R, Holtz Z et al. Whole body Positron Emission Tomography with 2-[18F]-Flouro-2-Deoxy-D Glucose can detect recurrent ovarian carcinoma. Gynecol Oncol 1993; 51: 175-181.*
20. *Bristow RE, Del Carmen MG, Pannu HK, et al. Clinically occult recurrent ovarian cancer: patient selection for secondary cytoreductive surgery using combined PET/CT. Gynecol Oncol 2003; 90(3):519-528.*
21. *Pomper MG. Functional and metabolic imaging. In: De Vita VT, Hellman S, Rosenberg SA, eds. Lippincot Williams and Wilkins, Philadelphia 2001: 679-688.*
22. *Kubik-Huch RA, Dorffler W, Von Schulthess GK, et al. Value of (18F) – FDG positron emission tomography, computer tomography and magnetic resonance imaging in diagnosing primary and recurrent ovarian carcinoma. Europ Radiol 2000; 10(5):761-767.*