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Cytoreductive Surgery for Advanced Tubo-ovarian Cancer – A Paradigm Shift

ABSTRACT

Complete macroscopic cytoreduction is the best prognostic variable a patient could experience during treatment for advanced ovarian cancer. Malta needs to make great strides to satisfy European-standard quality indicators for surgical management of advanced gynaecological cancer, and to progress toward 5-year survival rates of neighbouring countries. Surgical cytoreductive management requires a dedicated centralised team that can provide subspecialised multidisciplinary care. This article provides an overview of the role of cytoreductive surgery along the disease trajectory of advanced tubo-ovarian cancer.

KEYWORDS

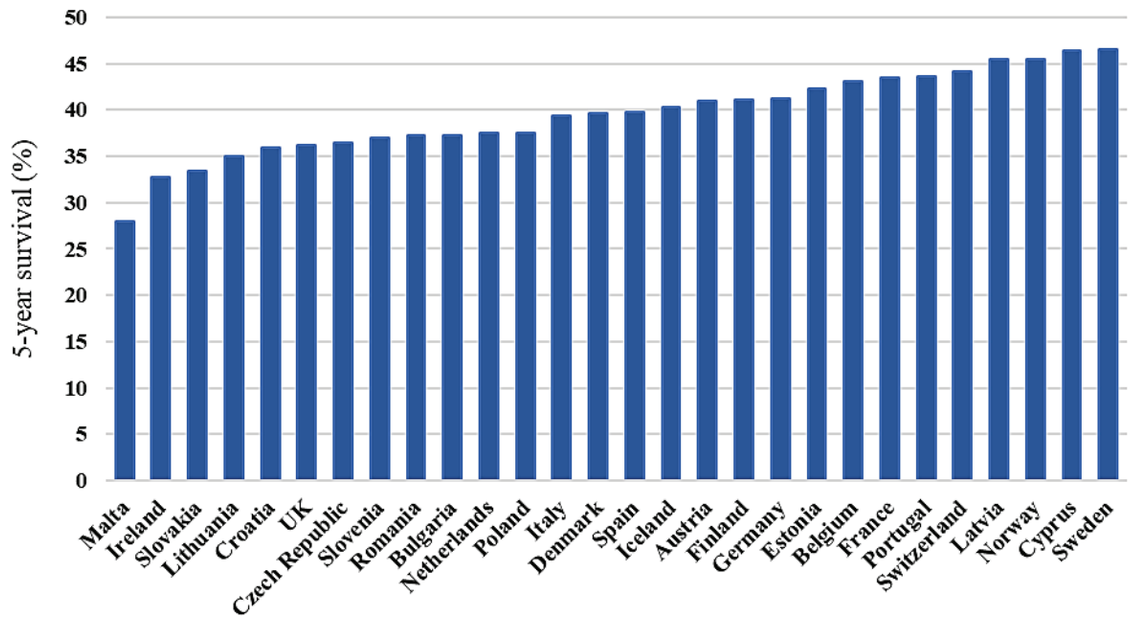
cytoreductive surgery, ovarian cancer, gynaecological oncology

BACKGROUND

Tubo-ovarian cancer represents the second most common gynaecological malignancy in Malta, with a local 5-year prevalence of 57 cases per 100,000, following uterine cancer with a 5-year prevalence of 138 cases per 100,000.[1] More than 75% of patients with tubo-ovarian carcinoma are diagnosed at an advanced stage of the disease, which is associated with poorer overall survival. Symptoms at presentation are vague and non-specific, contributing to late diagnosis. Meanwhile, only 20% of women with uterine cancer present with advanced disease. This is in part secondary to recognisable symptoms such as postmenopausal bleeding.

The CONCORD 3 collaborative project covering the period 2010-2014, showed that Maltese ovarian cancer patients had the lowest five-year age-standardised net survival (28%) of

Figure 1. Ovarian cancer 5-year age-standardised survival, Europe.[2]



THE CONCORD 3 COLLABORATIVE PROJECT COVERING THE PERIOD 2010-2014, SHOWED THAT MALTESE OVARIAN CANCER PATIENTS HAD THE LOWEST FIVE-YEAR AGE-STANDARDISED NET SURVIVAL (28%) OF ALL 31 COUNTRIES PARTICIPATING IN STUDY. THE TEMPORAL SURVIVAL TREND IS LESS THAN PROMISING; 5-YEAR SURVIVAL IN MALTESE OVARIAN CANCER PATIENTS WAS 34.2% IN 1995-1999, 39.6% IN 2000-2004 AND 27.5% IN 2005-2009

all 31 countries participating in study.[2] (Figure 1) The temporal survival trend is less than promising; 5-year survival in Maltese ovarian cancer patients was 34.2% in 1995-1999, 39.6% in 2000-2004 and 27.5% in 2005-2009.

Treatment for advanced gynaecological malignancies, particularly advanced ovarian cancer (AOC), consists of a combination of cytoreductive surgery and adjuvant treatment (such as chemotherapy), with maintenance treatment as appropriate (including agents such as Bevacizumab, Olaparib and Niraparib). Surgical cytoreduction, with the aim of achieving a state of no gross residual macroscopic disease, is the best prognostic variable a patient could experience throughout the disease trajectory. Each additional 10% cytoreduction of disease yields a 5.5% increase in median survival.[3]

Malignant epithelial ovarian tumours characteristically spread onto peritoneal surfaces via the transcoelomic route. Disease is expansile and characteristically respects peritoneal planes, enabling resection through a retroperitoneal approach. Localisation of peritoneal metastases is not random but is influenced by gravity, peritoneal fluid flow, peristalsis and peritoneal cavity recesses and ligaments. Spread typically occurs along the visceral and parietal peritoneal surfaces of the lower abdominal cavity, omental tissue, as well as diaphragmatic surfaces. Peritoneal fluid physiologically flows from the deep pelvis via the right paracolic gutter, cranially to Morison's pouch and right subdiaphragmatic space, and back down to the pelvis. For this reason, right-sided upper abdominal surfaces are more frequently involved in the disease process.[4]

A MULTIVISCERAL, MULTICOMPARTMENTAL APPROACH

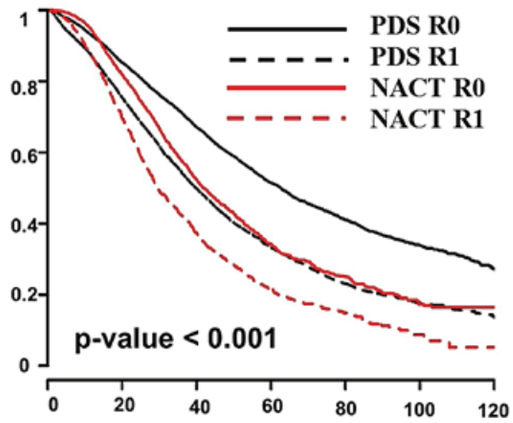
Several classifications enable the quantification of residual disease at cytoreduction. The most common terminology includes complete gross resection (CGR/R0 no residual macroscopic disease), optimal cytoreduction (R1<1cm residual disease) and suboptimal cytoreduction (R2 ≥1cm residual disease). The surgical objective for advanced gynaecological malignancy is that of achieving a CGR/R0 resection, as this is associated with the greatest progression-free survival (PFS) and overall survival (OS) benefit. In specific circumstances, an R1 resection may also confer a PFS and OS benefit. An R2 resection confers no PFS or OS benefit, but may provide palliation of symptoms from a specific disease site.

Achieving this target often requires a multivisceral, multicompartmental approach. Close to half the patients with advanced tubo-ovarian malignancy require a bowel resection (± enterostomy) to achieve CGR.[5] 39.5% of patients with advanced-stage disease require an upper abdominal resection - this includes right diaphragmatic stripping or full-thickness resection (29.3%), splenectomy (7.5%), lesser sac disease resection (5.4%) and porta-hepatis disease resection (5.4%).[6] Cases may also include the resection of enlarged pelvic, aortocaval, inguinal and/or cardiophrenic nodes. Routine resection of macroscopically normal lymph nodes in AOC is no longer recommended following the findings of the LION trial which showed this confers no PFS/OS benefit and is associated with a higher incidence of postoperative complications.[5]

SURGICAL TIMING

Several investigators have studied the impact of surgical timing on AOC patient outcomes. Surgery can be upfront (PDS, Primary debulking surgery), or may be undertaken halfway through chemotherapy (IDS, Interval debulking surgery). Delayed debulking surgery (DDS) is cytoreductive surgery after more than 5 cycles of chemotherapy. IDS and DDS need to be carefully timed to avoid surgery during the chemotherapy-induced nadir and associated

Figure 2. Impact of surgical timing on median survival (months) in AOC patients.[12]



Treatment sequence	Residual disease after surgery	Median survival	95% CI
PDS	R0	62.6	60.5, 64.5
	R1	39.8	38.6, 41.1
NACT	R0	41.8	40.2, 44.2
	R1	29.5	28.4, 31.9

complications such as anaemia, neutropenia and thrombocytopenia.

Major trials addressing surgical timing (EORTC[7], CHORUS[8] trials) showed that survival data for IDS are non-inferior to upfront surgery and this approach was associated with less surgical morbidity. A major criticism of these trials is that the maximal cytoreductive effort in their cohorts appears to be suboptimal, with a median operating time of less than three hours and CGR achieved in less than 20% of patients. The European Society of Gynaecological Oncology (ESGO) quality indicator for ovarian cancer cytoreductive surgery recommends a minimum CGR rate of 50% with an optimal target of >65%.[9] Malta's CGR rate between 2008-2016 was 9.5%.[10]

Evidence in the context of advanced uterine cancer, or AOC at DDS setting, has only shown an OS advantage with complete macroscopic resection. This means no statistically significant survival advantage is conferred with any residual disease at cytoreduction. Several proponents suggest that a maximal cytoreductive effort should be undertaken as early as possible if the patient is fit and the disease is deemed resectable on clinico-radiological assessment. At a physiological level, this means subsequent adjuvant chemotherapy would be targeting microscopic disease as opposed to gross tumour tissue. Surgery also eliminates cell subpopulations within the heterogeneic tumour environment, that could potentially become a chemo-resistant clone. Resection of ovarian tumour may also improve host immunity by removing from the host certain cells such as T-regulatory cells, which have known immunosuppressive properties.[11]

In a seminal paper titled 'Interval debulking surgery is not worth the wait' Lyons et al presented data from a cohort of 36,602 AOC patients, and showed that an R0 resection at PDS confers the best OS benefit, while an R1 resection at PDS is equivalent to an R0 resection at IDS (with prior neoadjuvant chemotherapy (*NACT*))[12] (Figure 2). ESGO quality indicators for AOC recommend >50% of cytoreductions should be at the PDS stage.[9]

The ongoing SUNNY[13] and TRUST[14] trials aim to re-investigate surgical timing and their protocols have emphasised standardised surgical quality and radicality for the participating teams.

The most common tubo-ovarian carcinoma subtype is high-grade serous adenocarcinoma which is associated with good chemotherapeutic response rate of over 70%. Upfront radical surgery is particularly important in chemo-resistant tumour subtypes such as low-grade serous adenocarcinoma, clear cell carcinoma and mucinous carcinoma.[15]

WHAT ARE THE LIMITS OF RESECTABILITY?

Specific disease sites are technically termed 'critical lesions' that should prompt a neoadjuvant chemotherapy approach (Figure 3). Preoperative radiological CT assessment is essential to identify patients at risk of a 'futile' (open-close) laparotomy or at a higher risk of residual disease following cytoreduction. However, a futile laparotomy at primary surgery does not mean a patient is ineligible to have an IDS/DDS attempt following treatment response to chemotherapy.

Figure 3. Critical lesions that preclude a primary cytoreductive approach in AOC patients.[9]

- Diffuse deep infiltration of the root of small bowel mesentery
- Diffuse carcinomatosis of the small bowel involving such large parts that resection would lead to a short bowel syndrome (remaining bowel <1.5 metres)
- Diffuse involvement/deep infiltration of:
  - stomach/duodenum
  - head or middle part of pancreas
- Involvement of coeliac trunk, hepatic arteries, left gastric artery
- Central or multisegmental parenchymal liver metastases
- Multiple parenchymal lung metastases (preferably histologically proven)
- Non-resectable lymph nodes

Quantifying the extent of bowel serosal and mesenteric deposits on CT is technically difficult to perform and report. One of the limitations of CT is its inability to demonstrate small volume 'miliary' (<5mm) deposits on the bowel serosa and mesentery, which are perhaps the most common rate-limiting steps precluding CGR. Evaluation may thus sometimes necessitate laparoscopic assessment to further assess disease distribution and resectability. Despite these limitations, with good imaging acquisition and interpretation, CT remains excellent with reported accuracies of 70-90% for detection of disease at all stages.[16] During gynae-oncological multidisciplinary meetings, a systematic CT reporting approach is essential to identify and communicate important sites of disease, which may alter treatment approach by the multidisciplinary team.[17] If a patient is not offered upfront surgery, a 'rate-limiting step' should be clearly documented in the multidisciplinary meeting outcome – this guides radiologists interpreting follow-up imaging when the case is being considered for IDS or DDS.

Following a systematic laparoscopy or exploratory laparotomy, the surgical team may in specific circumstances conclude that the risks of morbidity or quality of life impact of proceeding with maximal effort cytoreduction outweigh the benefits, based on the patient's clinical condition, frailty and the radicality required to achieve CGR. One may for example choose to abandon a primary cytoreduction attempt if achieving CGR would require a total colectomy and end ileostomy in a chemo-naïve patient, but may *not* reach the same conclusion if the patient has had neoadjuvant chemotherapy and is at IDS or DDS stage.

SECONDARY CYTOREDUCTIVE SURGERY

Following completion of primary AOC treatment, that is, a combination of surgical cytoreduction (PDS, IDS or DDS) and six chemotherapy cycles (generally Carboplatin + Paclitaxel ± Bevacizumab), the patient would then go onto maintenance treatment. This may include Bevacizumab (a VEGF inhibitor) or a PARP inhibitor such as Olaparib.

A majority of patients experience disease recurrence, at which point surgery also plays an important role. Surgery at this stage is termed secondary cytoreduction surgery (SCS). The landmark DESKTOP 3 trial showed a survival advantage in patients successfully undergoing SCS when compared to chemotherapy alone.[18] Among patients in the surgery arm who had complete tumour resection, the median overall survival was 61.9 months (95% CI 55.3-78.9), as compared with 27.7 months (95% CI 23.5-38.7) among patients who did not have complete resection, and 14 months (95% CI 12.7-15.4) in patients ineligible for SCS.

Not all patients with recurrent disease are eligible for SCS. DESKTOP 3 used the AGO criteria to assess patient eligibility: ECOG Performance status of 0, no residual disease at the initial cytoreductive surgery and ascites of <500ml on current imaging. Eligibility also requires relapsed disease to be at least 6 months after the last course of initial platinum-based chemotherapy e.g. carboplatin, cisplatin (i.e. platinum-sensitive disease). These criteria led to CGR in 76% of patients.[18] The most common recurrence sites at SCS are the pelvic peritoneum (34.4%), rectosigmoid serosa (31.3%), small bowel mesentery (25.0%) and small bowel serosa (20.3%). The proportion of women having bowel resection during SCS for recurrent epithelial ovarian cancer is quoted to be 29.7%.[19]

CONCLUSION

Tubo-ovarian cancer incidence is projected to increase by 5% over the next decade with an accompanying 15% decrease in mortality rate, reflecting population ageing and improved treatment strategies.[20,21]

A surgical team is as effective as the system that supports them. A multidisciplinary approach by appropriately trained professionals is necessary to improve outcomes for patients with advanced gynaecological malignancies such as AOC. This starts from preassessment, counselling and prehabilitation by dietetic teams, exercise physiologists, clinical nurse specialists and anaesthetic teams. It continues with appropriate support from non-gynaecological surgical specialities, as well as early postoperative monitoring within a high-dependency unit setting with input from physiotherapists, occupational therapists and other health care professionals.

In April 2023 NICE published its guidance supporting maximal cytoreductive surgery for AOC.[22] Several units have reported improved CGR rates and better AOC survival with homogenisation of care and centralised patient management by dedicated surgical gynae-oncology teams.[23] We need to tackle geographic disparities that exist in patient access to specialised gynaecological cancer care. Malta needs a paradigm shift in its surgical management of advanced gynaecological malignancies. Even when disease appears to be limited to the pelvis, surgery for suspected or confirmed ovarian cancer should only be undertaken with surgical preparedness to proceed with appropriate colorectal or upper abdominal procedures necessary to achieve CGR.

No conflicts of interest to declare.

EVEN WHEN DISEASE APPEARS TO BE LIMITED TO THE PELVIS, SURGERY FOR SUSPECTED OR CONFIRMED OVARIAN CANCER SHOULD ONLY BE UNDERTAKEN WITH SURGICAL PREPAREDNESS TO PROCEED WITH APPROPRIATE COLORECTAL OR UPPER ABDOMINAL PROCEDURES NECESSARY TO ACHIEVE COMPLETE GROSS RESECTION

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