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Continuous improvement in primary Debulking surgery for advanced ovarian cancer: Do increased complete gross resection rates independently lead to increased progression-free and overall survival?

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HIGHLIGHTS

- From 2001 to 2013, specific changes to our primary debulking surgery paradigm were implemented.
- Despite greater stage and tumor burden, complete gross resection (CGR) rates rose from 29% to 55%.
- 5-year progression-free survival (PFS) rates increased from 15% to 20%.
- Overall survival (OS) rates increased from 40% to 56%.
- CGR was independently associated with PFS and OS on multivariable analysis.

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ABSTRACT

Objectives. To assess complete gross resection (CGR) rates and survival outcomes in patients with advanced ovarian cancer who underwent primary debulking surgery (PDS) during a 13-year period in which specific changes to surgical paradigm were implemented.

Methods. We identified all patients with stage IIIB-IV high-grade ovarian carcinoma who underwent PDS at our institution, with the intent of maximal cytoreduction, from 1/2001–12/2013. Patients were categorized by year of PDS based on the implementation of surgical changes to our approach to ovarian cancer debulking (Group 1, 2001–2005; Group 2, 2006–2009; Group 3, 2010–2013).

Results. Among 978 patients, 78% had stage IIIC disease and 89% had disease of serous histology. Carcinomatosis was found in 81%, and 60% had bulky upper abdominal disease (UAD). Compared to Group 1, those who underwent PDS during the latter 2 time periods had higher ASA scores ($p < 0.001$), higher-stage disease ($p < 0.001$), and more often had carcinomatosis ($p = 0.015$) and bulky UAD ($p = 0.009$). CGR rates for Groups 1–3 increased from 29% to 40% to 55%, respectively ($p < 0.001$). Five-year progression-free survival (PFS) rates increased over time (15%, 16%, and 20%, respectively; $p = 0.199$), as did 5-year overall survival (OS) rates (40%, 44%, and 56%, respectively; $p < 0.001$). On multivariable analysis, CGR was independently associated with PFS ($p < 0.001$) and OS ($p < 0.001$).

Conclusions. Despite higher-stage disease and greater tumor burden, CGR rates, PFS and OS for patients who underwent PDS increased over a 13-year period. Surgical paradigm shifts implemented specifically to achieve more complete surgical cytoreduction are likely the reason for these improvements.

1. Introduction

Ovarian cancer is the leading cause of death among gynecologic malignancies. Approximately 22,240 women in the U.S. will be diagnosed with ovarian cancer in 2018, and an estimated 14,070 will die from

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this disease [1]. According to the National Cancer Institute, the 5-year survival rate for all stages of ovarian cancer is 47%. The rate, however, falls to 29% for those with distant metastases at the time of diagnosis [2].

Cytoreductive surgery with maximal tumor debulking is a key component of ovarian cancer treatment. In 1975, Griffiths published a landmark study demonstrating an inverse relationship between residual tumor burden and survival [3]. The greatest survival benefit was seen when resection of all visible tumor was achieved. Since then, multiple studies have confirmed that complete cytoreduction, also referred to as complete gross resection (CGR), is an important prognostic factor for survival [4–10]. In the absence of existing randomized controlled trials, a large systematic review of patients with stage III or IV ovarian cancer treated with primary debulking surgery (PDS) showed that complete cytoreduction was associated with significantly prolonged progression-free survival (PFS) and overall survival (OS) [11].

Most patients with ovarian cancer are diagnosed with advanced-stage disease, commonly with metastases to the omentum, small and large bowel, diaphragm, and upper abdominal (UAB) organs [2]. As the goal of PDS has evolved from debulking with <1–2 cm of residual disease to complete resection of all visible tumor, the role of complex surgery has become increasingly important. Several institutions have incorporated extensive surgical procedures into their practices, thereby successfully increasing CGR rates [12–16].

In pursuit of continual improvement in ovarian cancer outcomes, we questioned whether advances in preoperative and perioperative practices, in addition to expanding surgical extent, would further increase CGR rates and improve survival. Our institution implemented multiple advancements in our approach to ovarian cancer debulking surgery from 2001 to 2013. These included a shift in cytoreductive goal from <1 cm residual disease to no gross residual disease (CGR), performance of extensive UAB surgery and cardiophrenic lymph node dissection, alterations in patient selection, and modifications in operative start times. The primary objective of this study was to assess the changes in CGR rates and survival outcomes over the 13-year period during which these changes took place. Our secondary objective was to analyze whether the observed changes in CGR rates were independently associated with PFS and OS.

2. Methods

After obtaining Institutional Review Board approval for this single-institution, retrospective cohort study, we used the Memorial Sloan Kettering Cancer Center (MSK) Gynecology Service database to identify all patients with FIGO 2009 stage IIIB-IV ovarian, fallopian tube or primary peritoneal carcinoma who underwent PDS at our institution with the intent of maximal cytoreduction between 1/1/2001 and 12/31/2013. Patients who underwent exploratory laparotomy for anticipated debulking but who were ultimately declared unresectable due to extensive disease burden were still included in the analysis. The study was restricted to high-grade epithelial histologies. Those who received neoadjuvant chemotherapy (NACT) or presented for management of recurrent disease were excluded. We limited our analysis to patients who underwent PDS prior to 12/31/2013 to ensure adequate follow-up for calculation of 5-year survival.

Records for individual patients were reviewed and clinical variables were abstracted. *BRCA* mutation status was determined to be positive (genetic testing with evidence of deleterious *BRCA* mutation), negative (genetic testing without evidence of deleterious *BRCA* mutation), or unknown with/without a family history suggestive of hereditary breast and ovarian cancer (HBOC) syndrome. Patients meeting 1 or more of the following National Comprehensive Cancer Network (NCCN) criteria were deemed as having a positive family history: 1) one relative (1st, 2nd or 3rd degree) with either breast cancer diagnosed <age 50, 2 primary breast cancers, or male breast cancer; 2) one relative with ovarian, fallopian tube, or primary peritoneal cancer; 3) 2 relatives (same side of the family) with breast, pancreatic, and/or prostate cancer; or 4) known mutation within the family of a gene that increases susceptibility to cancer [17].

CGR was defined as no visible disease remaining at the end of the surgical procedure. Minimal residual disease (MRD) was defined as one or more tumor nodules 1–10 mm in maximal dimension remaining at the completion of surgery, and suboptimal debulking was defined as any residual tumor nodule >10 mm in maximal dimension remaining at the completion of surgery. Peritoneal carcinomatosis was deemed as present or absent according to the attending surgeon's operative note. If carcinomatosis was not specifically addressed in the operative note, it was defined as the presence of >20 tumor nodules within the abdominal cavity. Bulky UAB disease was defined as tumor implants >1 cm cephalad to the greater omentum. OR Tumor Index, a scoring system that reflects extent of disease based on a 0–2-point scale (carcinomatosis and bulky UAB disease each accounting for 1 point), was used to quantify disease burden [18]. Surgical adverse events occurring within 30 days of surgery were prospectively captured and graded according to the MSK institutional surgical secondary events grading system [19]. The date of recurrence/progression was determined by computed tomography (CT) scan. The appearance of one or more new lesions on CT scan, leading to a secondary debulking surgery or the initiation of a new chemotherapy regimen, was considered a recurrence. A change in treatment regimen due to an increase in size of an existing lesion was considered progression. The use of intraperitoneal (IP) chemotherapy was defined as administration of >1 cycle of IP treatment.

The study timeline was divided into 3 periods based on the implementation of changes to our institutional approach to ovarian cancer debulking, and patients were stratified into groups based on the year of their primary surgery: 2001–2005 (Group 1), 2006–2009 (Group 2), and 2010–2013 (Group 3). In 2001, we began to incorporate extensive UAB procedures into our debulking armamentarium [13]. In 2006, our goal for PDS evolved from residual disease <10 mm to either CGR or as minimal residual tumor as possible [7]. During 2010 to 2013, 3 additional changes were gradually adopted: routine performance of cardiophrenic lymph node resection [20], use of the selection criteria for NACT as described by Aletti et al. [21], and implementation of earlier operative start times [18]. The decision to define 2010 as the division point between Groups 2 and 3 was also influenced by the increase in our NACT rates after 2010 [22].

3. Statistical analysis

Differences in distribution among the patient groups were tested using the chi-square or Fisher exact test (if the cell count was <5) for categorical variables and the Kruskal-Wallis test for continuous variables. For 30-day/90-day mortality, short follow-up patients were excluded (0 excluded for 30-day mortality and 3 excluded for 90-day mortality).

PFS was defined as the time from the date of PDS to the date of recurrence/progression, death, or last follow-up, whichever occurred first. Both progression and death were considered events. OS was defined as the time from the date of PDS to the date of death or last follow-up, whichever occurred first. Death was considered an event. Median survival time and the 5-year survival rate were estimated using the Kaplan-Meier method.

The effect of residual disease on survival outcome was tested using the log-rank test. The associated hazard ration (HR) was obtained by fitting a Cox proportional hazards (PH) model without accounting for the institutional changes in the management of ovarian cancer over time. To examine the effect of PDS-year groups (reflecting the institutional changes in the management of ovarian cancer over time) on survival, we selected to test PFS and OS rates at the 5-year time point using a chi-square test with 2 degrees of freedom. The relevant point estimate and variance were obtained using the Kaplan-Meier method. To examine whether CGR was an

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