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ROLE OF MAXIMAL PRIMARY CYTOREDUCTIVE SURGERY IN PATIENTS WITH ADVANCED EPITHELIAL OVARIAN AND TUBAL CANCER: SURGICAL AND ONCOLOGICAL OUTCOMES SINGLE INSTITUTION EXPERIENCE

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To my family and my masters

Alla mia famiglia ed ai miei maestri

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INTRODUCTION

Epidemiology

Ovarian cancer is the ninth most common cancer in women (excluding skin cancer). It ranks fifth as the cause of cancer death in women. A woman's risk of getting invasive ovarian cancer in her lifetime is about 1 in 71 and the lifetime risk of dying from invasive ovarian cancer is about 1 in 95. In the United States, approximately 21,550 new cases and 14,600 deaths are estimated annually [1,2]. There are, however, large variations in the incidence of ovarian cancer in different areas of the world, in the European Union the estimated number of newly diagnosed cases was 42.700 in 2004 with a mortality of 12/100000 women/year [3]. The majority of these deaths were from ovarian cancer of the serous histological type and around half of women who are diagnosed with ovarian cancer are 60 or older.

Genetic predisposition for familial early-onset breast cancer accounts for approximately 5–10% of all breast cancers and 7–10% of all ovarian cancers [4]**.** Mutations in two autosomal dominant genes, *BRCA1* and *BRCA2*, have been linked to familial breast or breast and ovarian cancer [5,6]**.** Women who carry *BRCA1* or *BRCA2* mutations have an estimated lifetime risk of between 60% and 85% for developing breast cancer, and a lifetime risk of between 26% and 54% for developing ovarian cancer for *BRCA1*, and between 10% and 23% for *BRCA2* [7-10]**.** Although their mechanism of action is not yet fully elucidated, it is assumed that these genes play a key role in important cellular pathways including response to DNA damage, transcription, and interaction with other proteins involved in DNA repair and apoptosis [11,12] Genetic testing helps in identifying high-risk individuals in families with inherited breast and/or ovarian cancer, and there are various management options available for mutation carriers.

Etiology

Ovarian cancer has been associated with low parity and infertility. Although there have been a variety of epidemiologic variables correlated with ovarian cancer, such as talc use, galactose consumption, and tubal ligation, none has been so strongly correlated as poor reproductive history and duration of reproductive career. Early menarche and late menopause increase the risk of ovarian cancer. These factors and the relationship of parity and infertility to the risk of ovarian cancer have led to the hypothesis that suppression of ovulation may have an important role. Theoretically, the surface epithelium undergoes repetitive disruption and repair. It is thought that this process might lead to higher probability of spontaneous mutations that can unmask germline mutations or otherwise lead to the oncogenic phenotype.

Cancer is a genetic disease that results from a series of mutations in various cancer genes. Uncontrolled cancer growth occurs because of the accumulation of somatic mutations or the inheritance of one or more mutations through the germ-line followed by additional somatic mutations. The mutations in genes that are directly involved in normal cellular growth and proliferation can lead to the development of uncontrolled growth, invasion, and metastasis. Understanding the biology and molecular pathogenesis of ovarian epithelial tumors is the key of developing improved prognostic indicators and effective therapies. Data now suggest that high-grade serous tumors of the ovary differ from low-grade serous ovarian carcinomas in terms of their development, prognosis, pathology, and underlying molecular genetic alterations [13]. The main reason for the lack of success in effectively treating ovarian cancer is our limited understanding of its etiology and the very few molecular diagnostic markers and therapeutic targets known so far. Identification and characterization of ovarian cancer-associated genes are fundamental for unveiling the pathogenesis of its initiation and progression, especially the development of

recurrent diseases. If there was a way to determine “key drivers” of carcinogenesis which could address this issue, those patients with tumors amenable to surgical cytoreduction could be offered surgery as the initial therapy and the others (suboptimal) could be offered neoadjuvant therapy, followed by surgery. These “key drivers” could represent potential markers for prognosis and therapy. It has been suggested that early genetic events may direct the differentiation of ovarian epithelial cells. Decades of research have investigated molecular events such as: oncogenic activities of KRAS, BRAF, and AKT, and silencing mutations of TP53, RB, and PTEN that lead to ovarian cancer development. However, this information has had surprisingly little clinical impact on the outcome of women diagnosed with ovarian cancer. Recent evidence suggests that metastasis is an earlier event than previously thought and that only a very small number of shed malignant cells are capable of metastasizing (0.01%) [14,15].

The persistence of cancer cells in the vasculature does not necessarily result in seeding to distant sites and emerging evidence in breast cancer suggests that early tumors may already hold the genetic profile needed for metastasis. These early alterations in dominant genes may dictate the specific path that is followed with K-RAS leading to an LMP tumor and the early occurrence of a P53 or BRCA alteration leading to genetic instability and rapid progression to a high-grade phenotype. Characteristics common to both pathways include evasion of immune surveillance, invasion into the stroma, survival in the peritoneal cavity, attachment to intraperitoneal sites, and continued growth and angiogenesis [16]. What is urgently needed is an effective approach to rapidly and maximally leverage available ovarian cancer patient data to create an understanding of the disease that is detailed enough and accessible enough to enable “what if” queries regarding how best to treat patients with specific tumor characteristics, in terms of both genetics (the potential for disease outcome), disease biology (how the potential has played out up to the point of measurement), and the

connections between these and the clinical outcome, and can, in addition, incorporate the thousands of relevant variables.

Clinical presentation

Abdominal discomfort or vague pain, abdominal fullness, bowel habit changes, early satiety, dyspepsia, and bloating are frequent presenting symptoms. Occasionally, patients may present with bowel obstruction due to intra-abdominal masses or shortness of breath due to pleural effusion.

In early-stage disease, the patient may complain of irregular menses if she is premenopausal. If a pelvic mass is compressing the bladder or rectum, the patient may report urinary frequency and/or constipation. Occasionally, she may perceive lower abdominal distention, pressure, or pain, such as dyspareunia. Acute symptoms, such as pain secondary to rupture or torsion, are unusual. The presence of a pelvic mass at clinical evaluation is an important sign of possible ovarian cancer. Solid features, irregularity are the most important characteristics that suggest an ovarian cancer.

In advanced-stage disease, patients most often have symptoms related to the presence of ascites and abdominal distension due masses. The symptoms include abdominal distention, bloating, constipation, nausea, anorexia, or early satiety. In stage IV disease, a pleural effusion can be detected as well. If nodal metastases are present, inguinal, supraclavicular, and axillary nodes may be enlarged at palpation. Rarely, paraneoplastic syndromes may be present, including cerebellar degeneration associated with anti–Purkinje cell antibodies. Superficial thrombophlebitis, dermatomyositis, and polyarthritis have also been observed.

Rossing et al. [17], assessed the sensitivity, specificity, and positive predictive value of a proposed symptom index and of symptoms included for early detection of ovarian cancer. In-person interviews were conducted with 812 case patients who had epithelial ovarian cancer and with 1313 population-based control subjects. The symptom index was considered positive when pelvic or abdominal pain or bloating or feeling full was reported at least daily for at least 1 week, with an onset of less than 12 months before diagnosis or a reference date (for control subjects). The consensus criteria were considered fulfilled when any symptom above or urinary urgency or frequency was reported for at least 1 month, with an onset of less than 12 months before diagnosis or a reference date. Most case patients who had a positive index or met consensus criteria did so only within 5 months before diagnosis. Symptoms (except nausea) were somewhat less likely to have occurred among women diagnosed with early-stage than late-stage ovarian cancer. The estimated positive predictive value of the symptom index or symptoms meeting the consensus criteria was 0.6%-1.1% overall and less than 0.5% for early-stage disease. The authors concluded that the use of symptoms to trigger medical evaluation for ovarian cancer is likely to result in diagnosis of the disease in only one of 100 women in the general population with such symptoms.

Diagnosis

The serum CA-125 level has been widely used as a marker for a possible epithelial ovarian cancer in the primary assessment of a suspect adnexal mass. In this setting, false-positive results may derive from several conditions, especially those associated with peritoneal inflammation, such as endometriosis, adenomyosis, pelvic inflammatory disease, menstruation, uterine fibroids, or benign cysts. In a retrospective analysis of serum samples from 5550 women who were enrolled in a population-based registry in Sweden, 175 women had elevated CA-125 values. Ovarian cancer was ultimately diagnosed in six of these women and also developed in three women with normal CA-125 values. The specificity of the test was 98.5% for women over the age of 50 years but was lower (94.5%) for those who were younger than 50 (i.e., it had a low positive predictive value). As compared with women with an elevated CA-125 value in whom ovarian cancer was not diagnosed, the women who ultimately were found to have ovarian cancer were more likely to have progressive elevation of the CA-125 value over time [18].

Imaging of the ovary has been proposed as a strategy to detect changes in size and architecture that might precede the development of symptoms and detection by pelvic examination. Transvaginal ultrasonography is superior to transabdominal ultrasonography for detecting subtle details of ovarian structure and size. The use of size and morphologic characteristics of ovarian masses has been proposed to differentiate benign from malignant neoplasms [19]. In one study, in which measurement of ovarian volume, cyst-wall characteristics, and the presence of septae were used to calculate a risk score, the sensitivity was 89% and the specificity was 70%. Another morphologic index was reported to have a sensitivity of 100% and a specificity of 83% in differentiating benign from malignant lesions [20]. Several studies have evaluated pelvic ultrasonography to screen asymptomatic women for ovarian cancer. In a large prospective study, 25,327

women (including those over the age of 50 years who were at average risk and those over the age of 25 years with a family history of ovarian cancer) were screened with annual transvaginal ultrasonography. If an enlarged ovary was identified, its architectural features were described (cystic features, solid features, septations, papillations, nodules, or free peritoneal fluid). Among women with suspicious findings, surgical resection of the abnormal ovary was performed in 364 patients; 29 were found to have invasive ovarian cancer, among whom 14 (48%) had stage I disease. Nine patients received the diagnosis of ovarian cancer within 12 months after a negative ultrasonographic assessment. On the basis of stringent ultrasonographic criteria (i.e., unilocular ovarian cysts measuring less than 5 cm in diameter were not considered suspicious), the positive predictive value for ultrasonography was 27%, and the sensitivity was 85%. However, the fact that many patients were at high risk suggests that this positive predictive value is higher than the value that would be expected in the general population. Among women whose ovarian cancers were detected by screening, the 5-year survival rate was 77%, as compared with a rate of 49% in a historical control group from the same institution. However, the lack of randomization and an appropriate control group precludes a conclusion that screening resulted in improved survival [21].

Other imaging techniques, such as magnetic resonance imaging or positron emission tomography, may provide additional information but are not routinely necessary in preoperative evaluation. The goal of imaging in ovarian cancer detection is to expeditiously distinguish benign adnexal lesions from those requiring further pathologic evaluation for malignancy. For lesions indeterminate on ultrasound, MRI increases the specificity of imaging evaluation, thus decreasing benign resections. CT is useful in diagnosis and treatment planning of advanced cancer. Although (18) FDG-avid ovarian lesions in postmenopausal women are considered suspicious for malignancy, PET/CT is not

recommended for primary cancer detection because of high false-positive rates [22].

Staging and Risk Assessment

Surgical staging requires a laparotomy by a midline incision for an adequate exposure and careful examination of the abdominal cavity according to the Federation of Gynecology and Obstetrics (FIGO) guidelines (Figure 1). If disease appears confined to the ovary staging procedure includes biopsy of the diaphragmatic peritoneum, paracolic gutters, pelvic peritoneum, and complete or selected lymphadenectomy of the pelvic and para-aortic lymph nodes, and an infracolic omentectomy (are required, in addition) 4 washings of the peritoneal cavity (diaphragm, right and left sides of the abdomen, and pelvis); total abdominal hysterectomy and BSO; and appendectomy for mucinous tumors. Surgery should be carried out by an appropriately trained surgeon with experience in the management of ovarian cancer.

Several prognostic factors have been evaluated for epithelial ovarian cancers, which can be grouped into pathologic, biologic, and clinical factors. In general, histologic type is not of prognostic significance, with the exception of clear cell carcinomas, which (are) seem to be associated with a worse prognosis than the other histologic types.

More than 100 *protooncogenes* have been identified, and studies have focused on the amplification or expression of these genetic loci and their relationship to the development and progression of ovarian cancer. Additional prognostic variables include *p53, bcl-2*, k- *ras*, Ki67, interleukin-6, and platelet-derived growth factor. The relative prognostic value of individual factors is still undergoing evaluation [23-26].

In addition to stage, the extent of residual disease after primary surgery, the volume of ascites, patient age, and performance status are all independent prognostic variables [23].

Unfortunately, the only factor that the gynaecologist can influence is the amount of residual disease after the operation, and this makes adequate debulking one the most important aspect of ovarian cancer patient management, as subsequent therapies such as chemotherapy and radiotherapy are dependent upon the adequacy of the initial operative procedure.

Stage I - limited to one or both ovaries

- IA - involves one ovary; capsule intact; no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
- IB - involves both ovaries; capsule intact; no tumor on ovarian surface; negative washings
- IC - tumor limited to ovaries with any of the following: capsule ruptured, tumor on ovarian surface, positive washings

Stage II - pelvic extension or implants

- IIA - extension or implants onto uterus or fallopian tube; negative washings
- IIB - extension or implants onto other pelvic structures; negative washings
- IIC - pelvic extension or implants with positive peritoneal washings

Stage III - microscopic peritoneal implants outside of the pelvis; or limited to the pelvis with extension to the small bowel or omentum*

- IIIA - microscopic peritoneal metastases beyond pelvis
- IIIB - macroscopic peritoneal metastases beyond pelvis less than 2 cm in size
- IIIC - peritoneal metastases beyond pelvis > 2 cm or lymph node metastases

Stage IV - distant metastases to the liver or outside the peritoneal cavity

*Para-aortic lymph node metastases are considered regional lymph nodes (Stage IIIC).

Figure 1. FIGO Staging for carcinoma of the ovary

Surgical treatment

The standard approach to initial treatment of patients with advanced ovarian cancer (AOC) consist of primary cytoreductive surgery followed by combination platinum-based chemotherapy. Tumor reduction prior to chemotherapy may synchronize cell division, improve drug availability to metastases, reduce the number of cycles of chemotherapy required to eradicate residual disease, and diminish development of subsequent drug resistance.

Primary cytoreductive surgery has therefore become the cornerstone of the initial approach of patients with AOC. In 1975 Griffiths et colleagues [27], observed that patients who underwent surgical cytoreduction of bulky disease to small-volume disease had longer survival time than patients with larger-diameter disease. They proposed that their observation supported the Goldie-Coldman hypothesis, which states that small-volume tumors are less likely to develop chemotherapy resistance. Since 1986 the Gynecologic Oncology Group (GOG) has used the threshold of ≤1 cm residual disease in greatest dimension to define “optimal” cytoreduction [23,28], recently several reports have demonstrated that there may be an additional survival advantage associated with cytoreduction to no visible residual disease [29-34].

A literature review showed that patients with optimal cytoreduction had a median survival of 39 months compared with survival of only 17 months in patients with suboptimal residual disease. Hoskins et al., who presented data from the GOG showed that patients whose largest residual lesions were no greater than 10 mm had a superior survival [35]. Clearly, those patients whose disease has been completely resected have the best prognosis, and approximately 60% of patients in this category were free of disease at 5 years. Bristow et al. evaluated 81 studies involving 6885 patients and demonstrated that each 10% increase

in the number of patients receiving maximal cytoreduction was associated with a 5.5% increase in median survival [36].

Unfortunately many women with ovarian cancer do not undergo optimal surgery, one of the main reason is explained by numerous studies that have shown optimal cytoreduction rates grater than 50% often require the incorporation of a variety of extensive upper abdominal surgical procedures, not always affordable by general gynaecologists. Recently, accumulated evidence has suggested an associated survival benefit to these interventions in appropriate patients. Eisenhauer et al. [37] showed that in patients with stage IIIC and IV ovarian carcinoma who were optimally cytoreduced with the utilization of extensive upper abdominal surgery as diaphragm peritonectomy and/or resection, splenectomy, distal pancreatectomy, liver resection, etc., had improved survival compared to those who had suboptimal cytoreduction. Moreover, the PFS and OS of those patients who needed extensive upper abdominal procedures was identical to that of those who had less tumor volume and were able to be optimally cytoreduced with less-extensive surgery.

Studies have consistently shown that specialized surgeons, gynecologic oncologists, are more likely than general surgeons to perform optimal surgery for ovarian cancer [38].

The use of more extensive surgical approach has been associated with longer operative times, increased blood loss and transfusions, as well as higher morbidity [39].

Some investigators, such as Vergote et al. [40], have suggested to decreased morbidity with neoadjuvant chemotherapy. Pointing to an especially high complication rate and 6.2% of postoperative mortality during the period 1980-1988. They changed their approach in the time period between 1989 and 1997, 75 (43%) patients were surgically evaluated to receive primary chemotherapy and 98 (57%) underwent primary debulking surgery. They reported no postoperative mortality during the second time period and it was a statistically significant improvement in OS for the latter group. However, the two groups

received significantly different chemotherapy regimens. No patient in the earlier primary cytoreductive cohort received combination taxane and platinum-based therapy, 5% were treated with radiation therapy, and 19% received no treatment at all. In the latter cohort, 20% of patients received combination taxane and platinum-based chemotherapy and 3% of patients received no treatment. Furthermore, median OS for both groups was less than 36 months, which is inferior to contemporary studies [41-43]. While all these studies on neoadjuvant treatment demonstrate decreased morbidity, none of the studies advocating this approach have reported an equal or prolonged median survivals as opposed to the one reported in cohorts of patients undergoing primary optimal cytoreduction [41,42,44]. A recent meta-analysis of all neoadjuvant chemotherapy studies from 1989 to 2005 suggested that there may be an inverse relationship between the number of cycles o of neoadjuvant chemotherapy and OS [45].

Although a poor performance status, stage IV disease, and large number of metastatic implants on the mesenteric surface reduced the probability of achieving complete cytoreduction, the majority of patients with these findings still can undergo complete cytoreduction. Hence, it seems very difficult to define a group of patients for whom maximal operative effort would be impractical. Concerns about operative morbidity, reporting of outcomes that antedate descriptions of techniques that are necessary to achieve complete cytoreduction, and differences of opinion regarding the importance of cytoreduction may all account for the large percentage of patients who undergo incomplete resections.

If initial maximal cytoreduction is not carried out, interval debulking surgery (IDS) should be considered in patients responding to chemotherapy or showing stable disease. IDS should ideally be carried out after three cycles of chemotherapy, followed by three further cycles of chemotherapy.

Approximately 15% of epithelial ovarian cancer is diagnosed as stage IV disease. Overall, median survival for

patients with stage IV disease is approximately 15 to 23 months with an estimated 5-year survival of 20% [46].

A retrospective analysis of 360 patients with stage IV who underwent primary surgery followed by chemotherapy (6 cycles of intravenous platinum/paclitaxel) showed that patients with microscopic residual tumor after surgery had the best outcome; whereas patients with 0.1 to 1.0 cm residual disease and patients with 1.1 to 5.0 cm residual disease had similar progression free survival and overall survival. Furthermore ultra-radical cytoreduction might be justified in selected cases if microscopic residual tumor can be achieved [46].

Cytoreductive surgery seems to be the most important part of therapy for ovarian cancer, unfortunately, although we appear to be influencing the course of this disease by more aggressive therapy, radical debulking and intensive chemotherapy give widely differing results in different patients of the same stage, grade and cell-type. There are obviously other biological factors which we do not yet fully understand. Ways to be more selective with patients regarding therapy are urgently needed, but until then all medically fit patients deserve an aggressive, initial surgical approach.

OBJECTIVE

The objective of the present study was to determinate the impact of maximal cytoreductive surgery on progression free survival, overall survival rates and morbidity, in patients with advanced epithelial ovarian or fallopian tube cancer (stage IIIC-IV) treated in a referral cancer center

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, we reviewed all medical records of patients with stage IIIC–IV epithelial ovarian cancer who were managed at our institution between January 2001 and December 2008. Among these patients we identified all patients who underwent maximal primary cytoreductive surgery.

This specific study period encompassed the time when we changed our surgical approach with a more aggressive surgery incorporating extensive upper abdominal procedures that were defined as diaphragm peritonectomy and/or resection, splenectomy, distal pancreatectomy, partial liver resection, cholecystectomy and gastric resection performed only as necessary to achieve optimal cytoreduction. Optimal debulking was defined as no residual tumor nodule measuring greater than 10 mm in maximal dimension at the end of surgery.

Exclusion criteria included prior surgical exploration for cytoreduction at another institution, histology consistent with non-epithelial ovarian malignancies or borderline tumors. Patients with stage IIIC who had received neoadjuvant chemotherapy also were excluded.

Individual records were reviewed and the following information collected: age at surgery, date of surgery, American Society of Anestesiology (ASA) class, primary site of disease, presence of peritoneal carcinomatosis defined as tumor nodules covering the majority of surface of bowel serosa and the parietal peritoneum of the abdomen and pelvis, histologic type and tumor grade, pre-operative serum CA-125 level, location and size of the largest tumor mass, the initial ascites volume (if present), all surgical procedures performed, size of residual disease after surgery.

The surgical procedure included radical oophorectomy as the excision of internal reproductive organs en block with contiguous metastases and involved adjacent pelvic peritoneum. Modified posterior pelvic exenteration and rectal anastomosis were performed for invasion of the recto–sigmoid colon or extensive involvement of the sigmoid serosa in patients who could otherwise be rendered visibly disease-free. Omentum was removed at the level of the gastro–epiploic arcade. When extensively involved with tumor, a radical omentectomy was performed. When involved with tumor, the diaphragm was stripped or resected, or the implants were ablated. In case of diaphragm resection a chest tube was not placed routinely. When the spleen and/or distal pancreas were involved with tumor, a splenectomy with/without distal pancreatectomy were performed. The argon beam coagulator was used to ablate peritoneal and serosal metastases. Pelvic and/or para-aortic lymphnode dissection was performed mainly at the discretion of the primary surgeon to remove grossly involved lymph nodes and possible occult nodal disease. Patients with stage IV disease on the basis of liver or extra-abdominal lesions had these metastases resected whenever possible. Partial liver resection was performed in case of liver metastasis in patients who could otherwise be rendered visibly disease-free.

We classified the residual disease as follows: none grossly visible, gross residual 1-5 mm, 6-10 mm, 10-20 mm and >20 mm. These were the categories of residual disease used in the statistical analysis. Post-operative information as the estimated blood loss, number of transfused blood units, operative time, length of hospitalization, perioperative complications, type of adjuvant chemotherapy and number of cycles were also collected. All patients were staged by the International Federation of Gynecology and Obstetrics (FIGO) system.

Statistical analysis

Categorical variables were evaluated by $\chi 2$ analysis or Fisher's exact test, as appropriate, for category size. All statistical tests were two-sided, and differences were considered statistically significant at $P<0.05$. PFS was defined as the time interval from date of surgery to the date of the documented first recurrence of disease. If there was no documented recurrence, PFS was calculated from the date of surgery to the date of last follow-up or death, whichever occurred first. OS was defined as the time interval from date of surgery to the date of death or last follow-up. The Kaplan–Meier method was used to estimate survival curves and differences in survival were analyzed utilizing the log–rank test [47]. Cox proportional hazards regression was performed to identify independent prognostic variables for OS by univariate and multivariate analysis [48].

Continuous variables (age, CA-125, and ascites volume) were analyzed as categorical variables greater or less than the median value for the cohort. The factors analyzed included age ≤ or >60 years, ASA class, stage, histology, tumor grade, CA-125 ≤ or > 750 U/mL, ascites ≤ or >1000 cc, size and location of largest mass, presence of absence of peritoneal carcinomatosis, bowel resection, lymph nodal histology, and residual disease.

RESULTS

A total of 269 patients with advanced epithelial ovarian cancer were referred to our institution between January 2001 and December 2008, and of them 240 consecutive patients met inclusion criteria for the study. All these patients underwent an attempt of maximal surgical cytoreduction unless there was unresectable disease as determined by the attending surgeon.

The median age was 58 years (range 22 to 77 years). The final stage of disease was as follows: 187 patients (78%) had Stage IIIC disease, and 53 patients (22%) had Stage IV disease.

The distribution according to histological subtype was as follows: serous - (172/240) 72%, endometrioid - (35/240) 15 %, clear cell - (8/240) 3% and mixed - (24/240) 10%. The majority of patients 180/240 (75%) had grade 3 tumors, while 43/240 (18%) had grade 2 tumors, and 9/240 (4%) had grade 1 tumors (Table 1). Lymph node dissection (pelvic and/or para-aortic) was performed in 178/240 (74%) of the patients and 65% of these patients had positive lymph nodes at final pathology. Ascites was present at the time of surgery in 171 patients (71%) with a volume ranging between 100 cc and 15000 cc. Peritoneal carcinomatosis was present in 170/240 (71%), the majority of the patients presented the largest tumor mass at the level of pelvis, the median size was 13 cm with a range between 3 cm and 40 cm (Table 2).

All surgical procedures are listed on Table 3. The majority of patients underwent hysterectomy 226/240 (94%); rectosigmoid resection was performed in 143/240 (60%) as part of their radical pelvic tumor dissection. Additional bowel resections were performed in 51 patients (21%): small bowel resection in 12/240 (5%) patients, hemicolectomy in 22/240 (left, n=7; right, n=8; transverse, n=7), and 17/240 (7%) patients underwent ileocecal resection. Only one patient had a diverting colostomy while 2 received a diverting ileostomy at the time of surgery. The decision to place a diverting colostomy or ileostomy was at the operating

surgeon's discretion, and the reason for diversion was in all patients pre-operative bowel obstruction.

Complete cytoreduction to no gross residual disease was achieved in 111 patients, or 46 % of cases, while residual disease was ≤ 1 cm in 191 patients (80%), and 49 patients (20%) were left with residual tumor measuring >1cm in maximal diameter (Table 4).

The median EBL was 700 cc (range100 cc to 6000 cc) and the median operative time was 270 minutes (range 75 minutes to 480 minutes). 104 patients (43%) were transferred to the surgical intensive care unit post-operatively, with a median stay in the intensive care unit of 1 day (range 1 to 10 days). Blood transfusion, either intra-operatively or post-operatively, was administered to 157 (65%) of patients. Post-operative total parenteral nutrition was administered to 112/240 (47%) cases (Table 4).

There was no intra-operative death. Minor (defined as non-life-threatening) and major peri-operative complication occurred respectively in 37% and 21% of the patients (Table 6). Mild pleural effusion was observed in 45 patients of whom 75% had undergone peritoneal diaphragmatic stripping and/or resection. None of them required chest tube placement while it was necessary in 12 subjects who experienced symptomatic pleural effusion post-operatively. Postoperative re-exploration for haemoperitoneum occurred in 6/240 (2.5%) cases. Overall, 5 patients (3.4%) experienced a breakdown of the colorectal anastomosis, which was diagnosed from post-operative day 3 to post-operative day 6. Four patients were managed with surgical re-exploration and intestinal diversion, only one had resolution of bowel leakage with conservative management. Three fistulae were observed, one recto-vaginal and two involving the urinary tract. All of them were managed surgically. During peritoneal stripping incidental opening of the diaphragm occurred in 40% of the cases.

The median length of hospital stay was 9 days (range 4 to 30 days).

Post-operative platinum-based chemotherapy was administered in all patients; 221/240 (92%) were able to complete 5 or more cycles of platinum-based systematic chemotherapy (Table 4).

On univariate analysis (Table 7), factors significantly associated with decreased survival included: age grater than median (>60 years), presence of ascites >1000 cc, diffuse peritoneal carcinomatosis, omentum as anatomical location of the largest tumor mass, positive lymph-nodes and diameter of residual disease. ASA class, stage, tumor grade, histology, CA-125 greater than the median (> 750 U/mL), size of largest metastases bigger than 10 cm, and whether bowel resection was performed, did not significantly influence survival.

On multivariate analysis (Table 8) confirmed the independent association of age grater than 60 years and residual disease > 5 mm with worse survival.

In order to analyze more specifically the correlation between residual disease (no macroscopic RD) and different clinical and pathological variables, we performed a Pearson χ^2 analysis and logistic regression model (Table 9). At both the univariate and multivariate analysis the amount of ascites (< 1000 ml) and the absence of carcinomatosis were significantly associated with optimal residual disease. Age, ASA class and CA125 grater than 750 U/mL failed to achieve a statistical significance.

After a median follow up of 29.8 months, the overall median survival (OS) and progression free survival (PFS) were 61.1 and 20.4 months respectively (Fig. 2,3).

Figure 4 depicts the survival curves based on the various residual disease diameters at the end of surgery. Median overall survival in relation to the 5 residual disease categories was: no gross residual, not reached; gross 1- 5 mm, 61.3 months;5–10 mm, 44.8 months; 10–20 mm, 35.3 months; and >20 mm, 42.6

months. Kaplan-Meier survival curves comparing among the 5 residual disease categories revealed 2 distinct groups: these 2 groups were: (1) no gross residual and gross 1-≤ 5 mm ; (2) gross residual >5mm. There was a statistical significance difference toward improved survival in patients left with residual volume ≤0.5 mm compared with those belonging to the other groups of residual disease (*P* = 0.0019) Figure 5.

DISCUSSION

In 1934, Meigs published his work “Tumors of the female pelvic organs” [49] pointing out the possible benefits of primary cytoreductive surgery for advanced ovarian carcinoma as a means to enhance postoperative therapy. Later on Giffiths [27], in his seminal work demonstrated an inverse relationship residual tumor diameter and survival of the patients. Griffiths found that surgery provided optimum benefits when all gross tumor was excised, safely. This initial observation has been confirmed by multiple subsequent studies and it became the current treatment paradigm for patients with advanced ovarian cancer [36,50]. Therefore, the importance of a surgical cytoreduction in advanced ovarian cancer has become crucial, the debate over the definition of “optimal” versus “suboptimal” primary cytoreducion still remains objective of argument within the scientific community. The current definition of “optimal cytoreduction” was established in 1991 by the GOG in Protocol 97 as residual tumor ≤ 1 cm [23]. The definition of optimal cytoreduction has remained ≤1 cm in all subsequent GOG protocols. Nonetheless, very recent international cooperative studies have continued to use different definitions of “optimal” cytoreduction, indicating a lack of common consensus [51,52]. Recently several reports have demonstrated that there may be an additional survival advantage associated with cytoreduction to no visible residual disease [29-34].

Bristow et al. evaluated 81 studies involving 6885 patients and demonstrated that each 10% increase in the number of patients receiving maximal cytoreduction was associated with a 5.5% increase in median survival [36]

Several authors showed that the use of extensive upper abdominal surgical procedures significantly increased the optimal primary cytoreduction with a significant impact on the overall survival of these patients [53,54].

Chi et al. in a recent paper [55] analyzed the influence of upper abdomen surgery on progression-free survival and overall

survival in patients with stage IIIC and IV ovarian, tubal, and peritoneal cancer. The authors compared 2 different groups of patients, Group 1 (control group) consisted in 168 patients who underwent primary cytoreduction from 1/96 to 12/99. Group 2 (study group) consisted in 210 patients who underwent primary surgery from 01/01 to 12/04 including extensive upper abdominal procedures. The group 2 had a significant increase of optimal cytoreduction rate (80% vs 46%; *P*= <0.001), moreover the percentage of patients left with no grossly visible or palpable disease also increased from 11% in Group 1 to 27% in Group 2. The 5-year PFS rates for Group 2 vs Group 1 patients were 31% vs 14%, respectively (*P*=0.01). Five-year OS rates for Group 2 vs Group 1 patients were 47% vs 35%, respectively (*P*=0.03).

Similarly our surgical approach to patients with widespread of disease to the upper abdomen has changed since 2001 with the implementation of extensive upper abdominal procedures.

Among the 240 patients treated since 2001 the percentage of patients left with no grossly visible/palpable disease or residual disease ≤ 1 cm at the end of the primary surgery was 46% and 80% respectively.

Several authors raised the criticism that the improved survival of the patients undergone maximal cytoredution was determinate by a “good tumor biology”, as opposed to good surgical technique. [52,56]. During the study period almost 90% of the patients underwent surgery unless age, performance status or other medical conditions did not allow a general anaesthesia and an extensive surgery. Based on these criteria therefore we did not select a biologically more favourable group of patients.

Data from the Memorial Sloan Kettering Cancer Center showed that the amount of residual disease is one of the main prognostic factor. In fact, in a group of 465 patients with stage IIIC advanced ovarian cancer undergone primary cytoreductive surgery, they described a median overall survival in relation to the 5 residual disease categories as follows: no gross residual, 106 months; gross ≤0.5 cm, 66 months; 0.6–1.0 cm, 48 months; 1–2

cm, 33 months; >2 cm, 34 months. The Authors concluded that removal of all evidence of macroscopic disease is associated with prolonged survival and should be the goal of primary cytoreductive surgery [44].

The survival data calculated in the present study further support the reported observation that removal of all macroscopic disease has a statistically significant survival benefit. In our analysis of a wide distribution of patients with various residual disease sizes, patients with no gross residual disease and between 1-5 mm had a significantly (P=0.002) longer survival compared to the other category groups.

Moreover, regarding PFS, we found a statistically significant difference (P=0.028) between the group with no macroscopic residual disease (median of PFS of 29 months) and the other patients with any gross residual disease.

A major limitation of maximal cytoreductive surgery for ovarian cancer is that a minimal residual disease (≤ 1 cm) must be achieved at the end of surgery, but based on literature data, if this goal is not reached, surgery does not confer any appreciable survival benefit to patients and actually exposes them to long operative times, significant blood loss and transfusion rate, as well as higher morbidity.

The logical alternative claimed by supporters of “neoadjuvant” chemotherapy followed by interval debulking surgery consists in the attempt to reduce the bulk of neoplasia using chemotherapy to render the disease more amenable to subsequent surgical resection. Unfortunately the survival benefit of neoadjuvant chemotherapy has been shown to be significant worse than that of primary surgery. In fact, a review of the literature revealed that neoadjuvant chemotherapy approach decreases morbidity but none of the studies advocating this management have reported a median survival (range: 10.2-40 months) even close to the one (more than 60 months) reported for patient undergoing maximal cytoreductive surgery [57].

To this regards Vergote I [58], recently presented the results of a multicenter randomized clinical trial (EORTC 55791) on 718 stage IIIC-IV epithelial ovarian cancer patients, of them 668 met inclusion criteria: 329 were randomized to undergo primary debulking surgery (PDS) and 339 to receive neoadjuvant chemotherapy and followed by interval debulking surgery (IDS). Optimal cytoreduction (disease, ≤ 1 cm) was achieved in 46% of the cases in the first group, while in the IDS group it was achieved in 82%. Comparable percentages of patients received 6 cycles of chemotherapy (83% and 86% for PDS and IDS). Median follow up was 4.8 years. Progression free survival was equivalent in both groups (12 months) and median survival times were 30 months for patients who underwent primary surgery versus 31 months for patients treated with neoadjuvant chemotherapy followed by debulking surgery.

There are several limitations of the study, one of them being the low percentage of optimal cytoreduction obtained in the up-front surgery group, and the comparison with data of the literature and our owns (median PFS and OS of 20.4 months and 61.1 months respectively) shows remarkably different results compared to the EORTC study. The low rate (46%, ≤ 1 cm) of optimal residual disease at the end of surgery in PDS group has significantly worsened the prognosis of these patients.

Moreover we looked at the correlation between different variables and the rate of no evidence of macroscopic disease at the end of primary cytoreductive surgery. Patients with ascites >1000 ml and with peritoneal carcinomatosis were less likely to be optimally debulked suggesting that these factors could represent pre-operative selecting criteria for patients who might benefit from adjuvant chemotherapy approach.

Our study displays few weaknesses of our study are: this is a single-institution retrospective study, the post operative management after primary therapy was not perfectly homogenous and the follow-up interval is modest.

Moreover few patients during the first two years of the study (2001-2002) were treated prior to the implementation of upper abdominal surgery.

CONCLUSION

Our study seems to demonstrate that a more extensive surgical approach is associated with improved survival in patients with stages IIIC-IV epithelial ovarian cancer. Age grater than 60 years and residual tumor grater than 5 mm were independently associated with a worse prognosis. All patients with residual tumor ≤ 5 mm had the best prognosis as shown by the survival curves.
In view of these results we believe that the goal of primary surgery should be considered as leaving no macroscopic tumor or at least between 1-5 mm.

However in view of these findings gynaecologic oncologists must select carefully patients with advanced ovarian cancer and if complete gross resection is not feasible other therapeutic options must be considered. Future research should be directed at refining this model to more effectively stratify patients by likelihood of optimal resection, taking into account underlying health status and tumor dissemination

Table 1.
Patients and Tumor Characteristics.

Variable	No of patients (%)
Median Age (range)	58 years (22-77)
Primary site disease	
- Ovary	237 (98)
- Fallopian Tube	3 (2)
ASA class	
- 1-2	104 (43)
- 3-4	132 (55)
- NA	3 (2)
Figo Stage	
- IIIC	187 (78)
- IV	53 (22)
Tumor grade	
- 1-2	52 (22)
- 3	180 (75)
- NA	8 (3)
Histologic Type	
- Serous	172 (72)
- Endometrioid	35 (15)
- Clear cell	8 (3)
- Mixed	24 (10)
Median preop CA125 (range)	885.6 U/mL (17-52817)

Table 2.
Operative findings.

Variable	No of patients (%)
Diffuse peritoneal carcinomatosis	
- Yes	170 (71)
- No	70 (29)
Location of largest mass	
- Pelvis	127 (53)
- Omentum	98 (41)
- Upper Abdomen	11 (4.4)
- Retroperitoneal node	2 (0.8)
- Other	2 (0.8)
Size of largest mass (cm)	
- ≤ 10	90 (37.5)
- > 10	150 (62.5)
Median Ascites (range)	1500 cc (0-15000)
- ≤1000	114 (48)
- > 1000	125 (52)

Table 3.
Cytoreductive procedures.

Procedure	Number of patients (%)
Hysterectomy + USO/BSO	226 (94)
USO/BSO	14 (6)
Intestinal resection	
- Rectosigmoid resection	143 (60)
- Right hemicolectomy	8 (3.3)
- Left hemicolectomy	7 (3)
- Transverse colectomy	7 (3)
- Ileo-cecal resection	17 (7)
- Small bowel resection	12 (5)
Omentectomy	240 (100)
Appendectomy	104 (43)
Pelvic and/or Para-aortic lymph node dissection	144 (60)
Diaphragm stripping/resection	100 (42)
Cholecystectomy	4 (1.6)
Splenectomy	31 (13)
Partial liver resection	8 (3.3)
Distal Pancreasectomy	4 (1.6)
Gastric Resection	2 (0.8)

Table 4.
Surgical outcomes.

Variable	No of patients (%)
Residual disease (mm)	
- None grossly visible	111 (46)
- 1 - 5	47 (19.5)
- 5.1 - 10	33 (14)
- 11 - 20	16 (7)
- >20	33 (14)
Median length of surgery (range)	270 minutes (75-480)
Median estimated blood loss (range)	700 cc (100-6000)
Intra-operative blood transfusion	103 (43)
Post-operative blood transfusion	129 (54)
Intra-operative units blood transfused	40 (17)
- 1-2	25 (10.4)
- 3-4	9 (4)
- > 5	
Post-operative units blood transfused	103 (43)
- 1-2	22 (9)
- 3-4	4 (2)
- > 5	
Length of hospitalization (days)	
- ≤ 4	9 (4)
- 5 – 7	65 (27)
- 8 – 10	85 (35)
- > 10	81 (34)
Length of ICU* (days)	
- 1 – 2	91 (38)
- 3 – 4	8 (3)
- > 5	5 (2)
Total Parenteral Nutrition (TPN)	
- Yes	112 (47)
- No	128 (53)
Systematic chemotherapy platinum-based Completed ≥ 5 cycles	221 (92)

* Intensive Unit Care

Table 5.
Intra-operative morbidity.

Complication	**No**	**%**
Gastrointestinal lesion	1	0.4
Vascular lesion	1	0.4
Urologic lesion	8	3.3
Total	**10**	**4**

Table 6.
Peri-operative morbidity.

Minor Complication	**No**	**%**
Postoperative Ileus	7	3
Wound infection	17	7
Urinary tract infection / pyelonephritis	5	2
Neurologic	5	2.9
Pneumonia	4	1.6
Mild Pleural effusion	45	18
Mild Pneumothorax	7	2.9
Total	**90/240**	**37**
Major Complication	**No**	**%**
Anastomotic Leak	5	3.5
Anastomotic Stenosis	2	1.4
Pelvic abscesses	4	1.6
Fistulas	3	1.2
Bacteremia/sepsis	7	2.9
Haemoperitoneum*	6	2.5
Pleural effusion°	12	5
Deep vein thrombosis/ pulmonary embolism	6	2.5
Cardiovascular (heart attack)	4	1.6
Neurologic (brain stroke)	2	0.8
Total	**51/240**	**21**

* All patients required a re-intervention
° All patients required thoracic drain post-operatively

Table 7.
Univariate analysis of categorical variables determining survival.

Factor	No of patients	Dead No. (%)	Hazard Ratio (95% CI)	*P* value
Age				
- ≤ 60	132	45 (34)	1 (ref)	
- > 60	108	51 (47)	1.76 (1.17,2.64)	**0.006**
ASA				
- 1-2	104	32 (31)	1 (ref)	
- 3-4	132	63 (48)	1.07 (0.68,1.66)	0.78
Stage				
- IIIC	187	73 (39)	1 (ref)	0.52
- IV	53	23 (43)	1.17 (0.72, 1.89)	
Grade				
- 1-2	52	27 (52)	1 (ref)	0.62
- 3	180	67 (37)	0.89 (0.57,1.40)	
Histology				
- Serous	172	67 (39)	1 (ref)	
- Endometriod	35	13 (37)	0.94 (0.52,1.70)	0.83
- Clear cell	8	3 (37)	1.48 (0.46,4,73)	0.51
- Mixed	24	12 (50)	1.51 (0.80,2.86)	0.20
Ascites				
- ≤ 1000 cc	114	38 (33)	1 (ref)	
- > 1000 cc	125	58 (46)	1.63 (1.08,2.46)	**0.02**
CA125				
- ≤ 750 U/mL	110	38 (34)	1 (ref)	
- > 750 U/mL	128	57 (44)	1.17 (0.77,1.77)	0.47
Size of Largest Mass				
- ≤ 10 CM	90	30 (33)	1 (ref)	
- > 10 CM	150	66 (44)	1.43 (0.93,2.22)	0.11
Diffuse peritoneal carcinomatosis				
- No	70	17 (24)	1 (ref)	
- Yes	170	79 (46)	2.37 (1.40,4.00)	**0.001**
Location of largest mass				
- Pelvis	127	42 (33)	1 (ref)	
- Omentum	98	49 (50)	1.70 (1.12,2.58)	**0.014**
- Upper Abdomen	11	11 (100)	1.29 (0.46,3.59)	0.63
- Nodes	2	1 (50)	na	
- Other	2	0 (0)	na	
	-	-	na	
Bowel Resection				
- No	96	31 (32)	1 (ref)	0.14
- Yes	144	65 (45)	1.39 (0.90, 2.14)	
Nodes				
- Negative	30	5 (16)	1 (ref)	
- Positive	148	65 (44)	3.14 (1.26,7.82)	**0.014**
Residual disease				
- None grossly visible	111	26	1 (ref)	
- 1 – 5 mm	47	19	1.67 (0.92,3.02)	**0.089**
- 5.1 – 10 mm	33	22	2.08 (1.18,3.68)	**0.018**
- 11 – 20 mm	16	12	2.55 (1.26,5.16)	**0.009**
- >20 mm	33	17	2.34 (1.27,4.32)	**0.006**

Table 8.
Multivariate Analysis of Survival

Covariate	Risk ratio (95% CI)	*P* value
Age		
- ≤ 60 years	1 (ref)	
- > 60 years	1.67 (1.10,2.53)	**0.014**
Ascites		
- ≤ 1000 cc	1 (ref)	
- > 1000 cc	1.33 (0.86,2.06)	0.19
Residual disease		
- None grossly visible	1 (ref)	
- 1 – 5 mm	0.32 (0.73,2.51)	0.32
- 5.1 – 10 mm	1.85 (1.02,3.32)	**0.04**
- 11 – 20 mm	2.35 (1.15,4.80)	**0.018**
- >20 mm	2.05 (1.09,3.86)	**0.024**

Table 9.
Correlation between different clinical and pathological variables and residual disease.

	% optimal cytoreduction (no macroscopic RD)	***P* value (Univ)**	***P* value (Multiv)**	**Odds ratio (95% CI)**
Age (≤ 60 vs >60)	59 VS 40	0.20	0.31	1.37 (0.75,2.54)
ASA (1,2 vs 3,4)	55 VS 45	0.002	0.14	1.61 (0.86,3.00)
CA 125 (≤ 750 U/mL vs > 750 U/mL)	57 VS 43	0.002	0.80	1.09 (0.57,2.09)
Ascites (≤1000 cc vs > 1000 cc=)	67 VS 33	**< 0.001**	**0.049**	**1.95 (1.00,3.80)**
Carcinomatosis (no vs yes)	53 vs 47	**< 0.001**	**< 0.001**	**9.01 (4.08,19.9)**

Figure 2.
Overall Survival

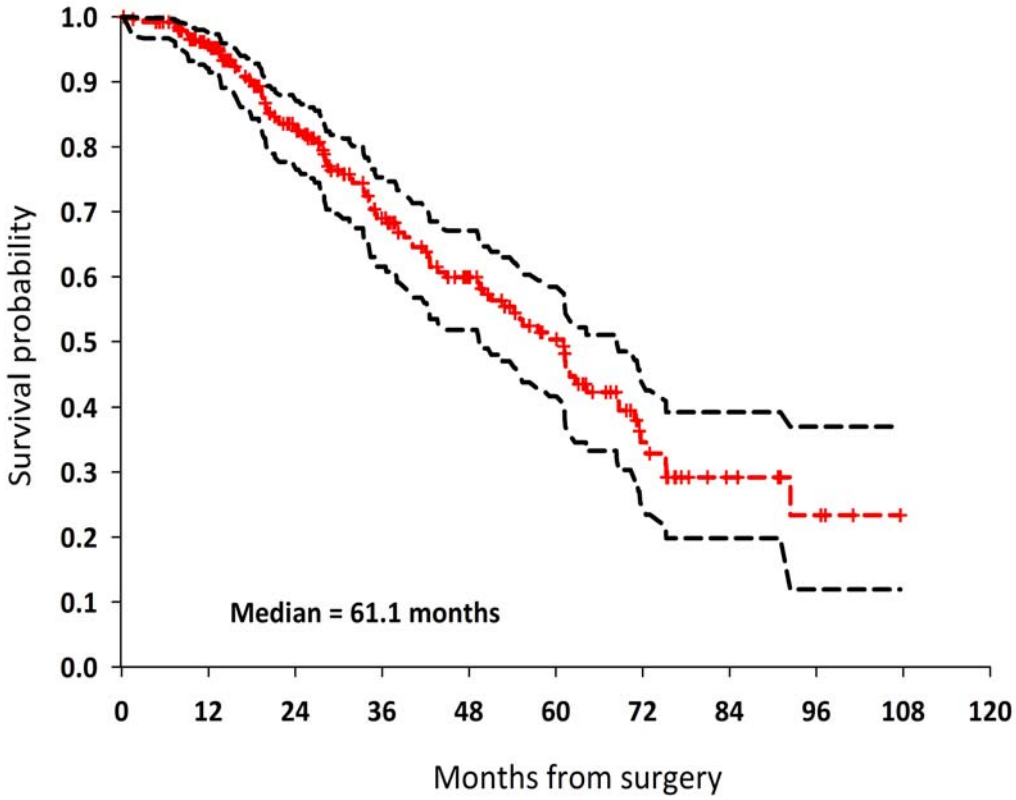


Figure 3.
Progression Free Survival

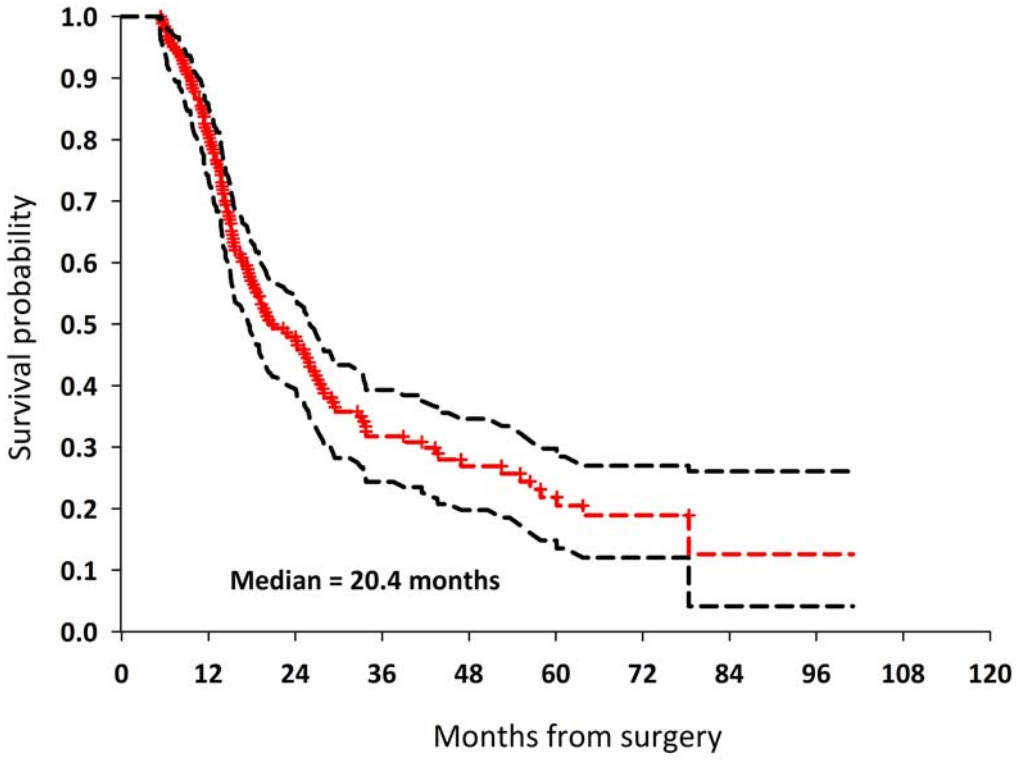


Figure 4.
Overall Survival by Residual Tumor Size

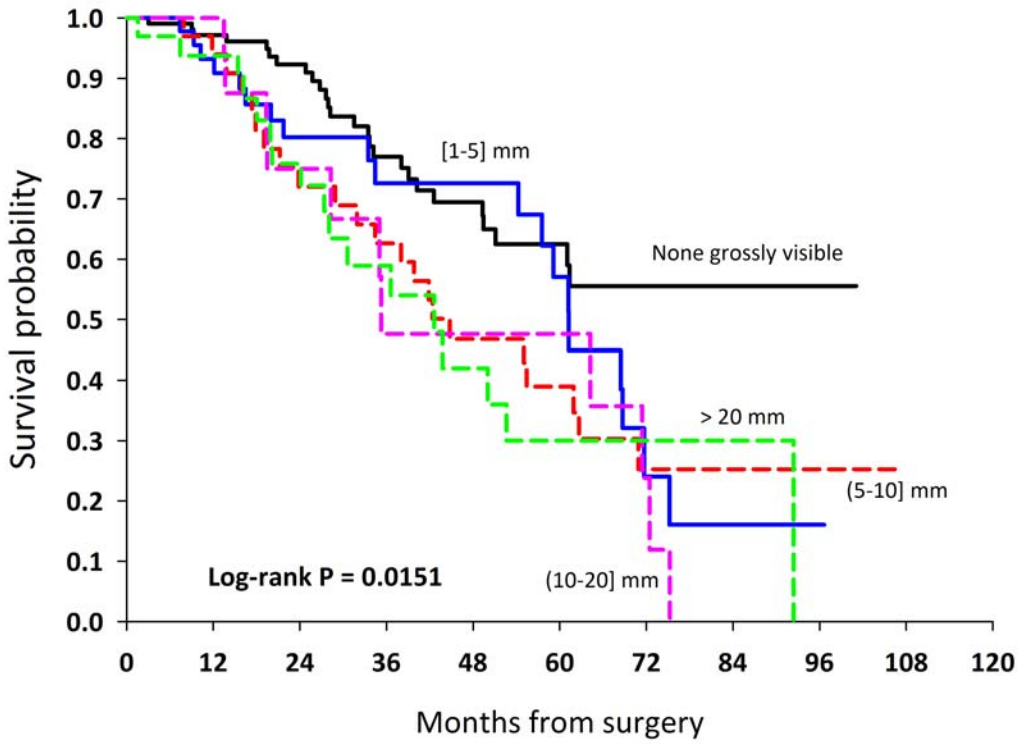
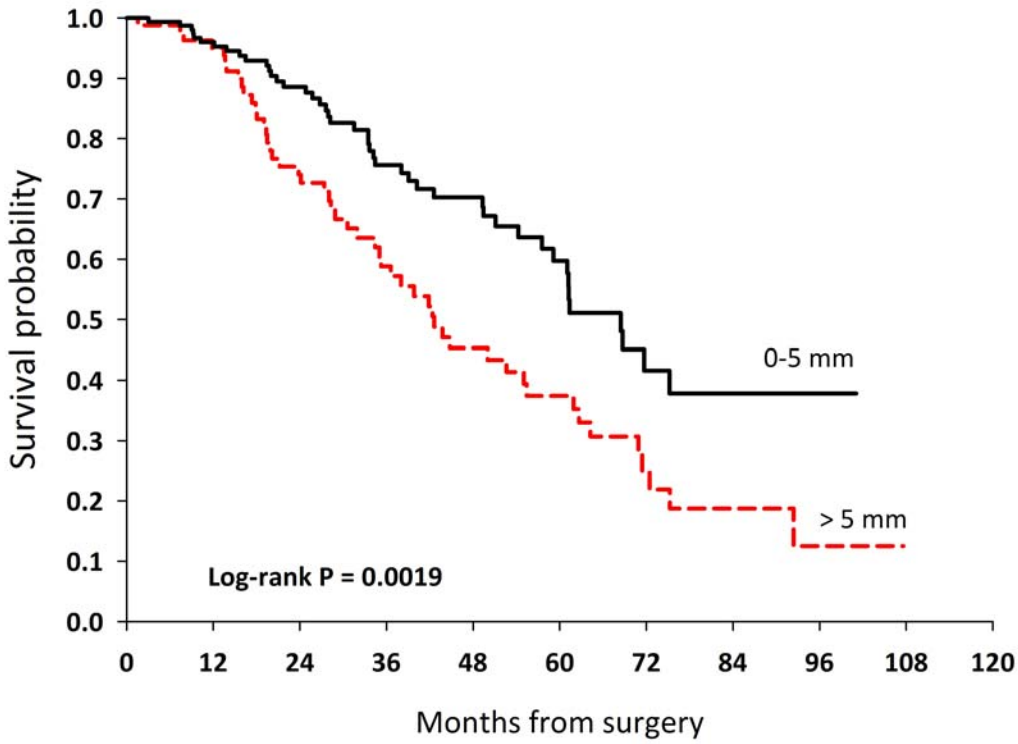


Figure 5.
Overall Survival by Residual Tumor Size



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