Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

A comparative analysis of prediction models for complete gross resection in secondary cytoreductive surgery for ovarian cancer

Renee A. Cowan [a], Ane Gerda Zahl Eriksson [a], Sara M. Jaber [a], Qin Zhou [b], Alexia Iasonos [b], Oliver Zivanovic [a,c], Mario M. Leitao Jr [a,c], Nadeem R. Abu-Rustum [a,c], Dennis S. Chi [a,c], Ginger J. Gardner [a,c,*]

[a] Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[b] Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[c] Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY, United States

HIGHLIGHTS

- Examine 3 predictive models for secondary surgery in recurrent ovarian cancer
- Complete gross resection during secondary surgery may extend PFS and OS.
- Some criteria may be too strict, prohibiting patients from beneficial intervention.

ARTICLE INFO

Article history:
Received 17 November 2016
Received in revised form 2 February 2017
Accepted 5 February 2017
Available online xxxx

Keywords:
Ovarian cancer
Prediction models
Secondary cytoreductive surgery
Complete gross resection
AGO DESKTOP criteria
Tian model

ABSTRACT

Objective. We sought to examine compliance and outcomes using Memorial Sloan Kettering "(MSK) criteria" to predict complete gross resection (CGR) and compare them with the validated Tian and AGO models.

Methods. Patients who underwent SCS for recurrent platinum-sensitive ovarian cancer from 5/2001–6/2014 were identified. The AGO and Tian models were applied to the study population; appropriate statistical tests were used to determine ability to predict CGR.

Results. 214 SCS cases were identified. Since the implementation of MSK criteria, the CGR rate has been 86%. The AGO model had a 49% accuracy rate in predicting CGR, and predicted gross residual disease (RD) in 51%; however, CGR was achieved in 86%. The Tian model had an 88% accuracy rate. Of the 4% scored as Tian high risk for gross RD, 33% achieved a CGR. Comparing models, McNemar's p-value was 0.366 between the Tian and MSK models and <0.001 between AGO and MSK criteria. Median PFS was 21.3 (95%CI, 18.2–24.5), 22.5 (95%CI, 19.4–25.3), and 14.1 months (95%CI, 9.7–22.1) for the entire cohort, for those achieving CGR, and for those left with RD, respectively ($p = 0.013$). OS was 82.2 (95%CI, 60.2–123.3), 95.6 (95%CI, 63.6–NE), and 57.5 months (95%CI, 27.5–113.9), respectively ($p = 0.014$).

Conclusion. CGR during SCS is associated with extended PFS and OS. We report a high rate of CGR using MSK criteria. There was good concordance between the Tian and MSK models; however, the latter has fewer variables and is more user-friendly. Tian criteria may be applied to intermediate MSK cases for further stratification.

1. Introduction

The cornerstone of the initial management of ovarian cancer includes surgical resection and combination chemotherapy. Despite the advances in this treatment model and the initial successful response of most patients, 75–80% of women will recur [1]. Disease recurring ≥6 months after completion of platinum-based therapy is deemed "platinum sensitive". Currently, combination platinum-based chemotherapy with or without target-based agents is the mainstay of care for platinum-sensitive recurrent ovarian cancer (ROC) [1–3].

However, there is evidence showing that secondary cytoreductive surgery (SCS) may have a place in the treatment of ROC. In 1983, Berek et al. were among the first to describe their experience with 32 patients treated with SCS for ROC [4]. Since then, there have been numerous studies reporting the benefits of SCS but no published randomized control trials comparing surgery followed by chemotherapy to chemotherapy alone [5]. SCS can be beneficial in select patients in whom complete gross resection of macroscopic disease (CGR) is achieved [6]. The criteria for the selection of these patients, however, vary widely. Because of this variation, CGR rates also widely vary, with

* Corresponding author at: Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, United States.
E-mail address: gardnerg@mskcc.org (G.J. Gardner).

http://dx.doi.org/10.1016/j.ygyno.2017.02.010
0090-8258/

a weighted mean of 52.5% [6]. A validated model could help ensure appropriate patients are selected for SCS while sparing non-candidates SCS-associated morbidity.

In 2006, both Chi et al. and the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian (AGO-OVAR) Committee published criteria and recommendations for SCS patient selection [7,8]. In 2012, Tian et al. created a mathematically based model [9]. The objective of our study was to examine compliance and current outcomes using our institutional model, the "MSK criteria," to predict CGR, and compare its performance with the most often cited internationally validated models—the Tian model and AGO DESKTOP criteria.

2. Methods

2.1. Study population

After IRB exemption was obtained, we collected the demographic, clinical, pathologic, and outcome data for all patients treated with SCS for recurrent platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancers from 5/2001–6/2014. Patients who received chemotherapy for their recurrence prior to SCS were excluded. Patients were also excluded if they had borderline tumors or their secondary surgery was not performed with the intent of CGR, such as bowel obstruction or palliative indications. Complications were graded according to an institutional surgical complication grading system [10]. Perioperative complications and death were defined as any adverse event related to operative treatment occurring within 30 days of surgery. If there was more than one complication, the highest-grade complication was used for analysis. No patients in this population were used to create the models in this study.

2.2. Model selection for comparative performance analysis

Using the keywords "recurrent ovarian cancer," "secondary cytoreductive surgery," and "prediction models," a Scopus database search was conducted for articles publishing, evaluating, or validating predictive models or criteria for SCS patient selection. While the search generated multiple models, the AGO Score and the Tian model were the only ones externally validated [11–15]. Two newer models were published in 2015—the SeC-Score and the Minaguchi criteria—but both were excluded, because they had not been externally validated [16,17]. Furthermore, the SeC-Score requires an HE4 level, which is not universally available in this patient population.

Chi et al. published a retrospective review of 153 patients who had undergone SCS form 1987–2001 [7] and showed a CGR rate of 41%. Based on their analyses, SCS is recommended for all patients with a single site of recurrence, regardless of disease-free interval (DFI); patients with multiple sites of recurrence but no carcinomatosis and DFI > 12 months; and patients with carcinomatosis but DFI >30 months (Supplemental Table 1).

The AGO-OVAR DESKTOP Trial was a study of over 260 patients from 25 different centers in Germany and Switzerland who had undergone SCS for a primary recurrence from 2000 to 2003. CGR was achieved in approximately 50% of patients. From their analyses, they created a set of criteria in which patients with platinum-sensitive disease who had a good performance status (Eastern Cooperative Oncology Group [ECOG] = 0), no residual tumor after primary surgery, and no or small-volume ascites (<500 mL) were considered score "positive" and appropriate candidates for SCS. Multiple studies have validated the positive predictive value (PPV) of this model, while also reporting high false-negative rates [8,11–15] (Supplemental Table 2).

Tian et al. sought to better assess the variables associated with CGR in SCS by collecting raw data from nine studies previously published, including the Chi and AGO data [9]. CGR was achieved in 40% of the population, with rates ranging from 8.3–65.9%. Their multivariate logistic regression identified six significant variables: International Federation of Gynecology and Obstetrics (FIGO) stage, residual disease (RD) after primary cytoreduction, ECOG performance status, DFI, CA-125, and the presence of ascites at recurrence. They assigned each variable a risk score based on the beta coefficient obtained from the logistic regression. The sum of a patient's risk scores would then designate the patient low risk (≤4.7) or high risk (>4.7). The low-risk group would be more likely to achieve CGR at SCS. This model has been validated, but also has reports of a high false-negative rate [13,15] (Supplemental Table 3).

Table 1
Patient and tumor characteristics ($N = 214$).

Characteristic	No. of patients (%)
Primary tumor site	
Ovary	179 (84)
Fallopian tube	21 (10)
Peritoneum	14 (7)
FIGO stage	
I/II	51 (24)
III/IV	163 (76)
Tumor histology	
High-grade serous	162 (76)
High-grade endometrioid	13 (6)
Low-grade serous	12 (5)
Low-grade endometrioid	2 (1)
Clear cell	6 (3)
Other	19 (9)
Initial method of detection of recurrence	
CA-125	96 (45)
Imaging	89 (42)
Physical exam	25 (12)
Other	4 (2)
Residual after primary cytoreduction	
0 cm	101 (54)
>0 cm and ≤0.5 cm	33 (18)
>0.5 cm and ≤1 cm	30 (16)
>1 cm	24 (13)
Performance status	
0	182 (85)
1	32 (15)

FIGO, International Federation of Gynecology and Obstetrics.

2.3. Statistical analysis

Data on patient and tumor characteristics, operative findings, outcomes of SCS, progression-free survival (PFS), and overall survival (OS) were documented. RD was recorded as the greatest diameter (cm) of the largest residual tumor nodule as documented in the operative report. PFS was calculated from the SCS date to the date of second progression, death, or last follow-up. OS was defined as time elapsed in months from SCS date to the date of death or last follow-up. Follow-up data were collected until August 2015. The Kaplan-Meier method was used to generate survival curves [18]. The MSK, AGO, and Tian models were applied to this population, and PPV, negative predictive value (NPV), sensitivity, specificity, accuracy, Kappa coefficient, and McNemar's test were computed to determine their performance in predicting CGR [19,20].

3. Results

3.1. Patient characteristics

Two hundred fourteen patients who met inclusion criteria were identified. The primary surgeon in all SCS cases was an attending gynecologic oncologist. Median age at the time of recurrence was 58.5 years (range, 22–86). Median CA-125 at time of recurrence was 28 (range, 2–3357). "Initial method of detection" refers to the inciting event that triggered further investigation to evaluate and confirm disease recurrence. Case characteristics are listed in Table 1.

Please cite this article as: R.A. Cowan, et al., A comparative analysis of prediction models for complete gross resection in secondary cytoreductive surgery for ovarian cancer, Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.02.010