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Review Article

Prognostic significance of lymphadenectomyin malignant ovarian sex cord stromal tumor: A retrospective cohort study and meta-analysis

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HIGHLIGHTS

- SCSTs are rare neoplasms accounting for approximately 5–7% of all ovarian malignancies.
- The lymph node metastasis rate in SCSTs is extremely low.
- Lymphadenectomy has no statistical significance in improving overall survival.

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ABSTRACT

Objectives. To evaluate the prognostic significance of lymphadenectomy in malignant ovarian sex cord stromal tumor (SCST).

Methods. The medical records of patients with malignant ovarian SCST who underwent primary surgery from April 2005 to December 2016 were retrospectively reviewed in the Department of Obstetrics and Gynecology of Qilu Hospital. A meta-analysis was performed by searching the PubMed and Embase database up to July 20, 2017. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by STATA statistical software version 19.0.

Results. Seventy-two patients with malignant SCST were identified in our institution. The mean age of the patients was 44.3 years (range, 8–80 years). Among the 72 patients, 69.4% had granulosa cell tumors (GCTs, $n = 50$); 47.2% ($n = 34$) underwent lymphadenectomy, and 52.8% ($n = 38$) did not undergo the surgery. None of the lymph nodes had pathologically confirmed metastasis. No significant differences in overall survival of the patients with SCST or GCT were noted based on patient age, tumor size, surgery extent, or administration of cytotoxic chemotherapy, except tumor stage ($P = 0.010$ in SCTs and 0.029 in GCTs, respectively). Lymphadenectomy showed no statistically significant difference in overall survival of patients with SCST or GCT ($P = 0.734$ and 0.079, respectively).

In our meta-analysis, a total of 179 studies were identified through a search strategy, and 13 studies were included eventually; 3223 cases were identified, including those from our institution. The random-effects model was used because of moderate heterogeneity ($I^2 = 43.8\%$, $P = 0.040$). The estimated pooled OR was 0.87 (95% CI, 0.57–1.31), indicating that lymphadenectomy has no statistical significance in improving overall survival in SCSTs ($Z = 0.68$, $P = 0.496$).

Conclusions. Tumor stage is the most important prognostic factor affecting SCST overall survival. There is no significant effect of lymphadenectomy in improving the overall survival of SCSTs. Lymphadenectomy is not recommended in initial staging surgery of SCST due to the extremely low lymph node metastasis rate.

Contents

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1. Introduction

Sex cord stromal tumors (SCSTs) are rare neoplasms, accounting for approximately 5–7% of all ovarian malignancies, and most of them are granulosa cell tumors (GCTs) [1–6]. These tumors arise from sex cord cells and secrete hormones that usually cause bleeding or amenorrhea. Other typical symptoms include adnexal mass and abdominal pain [7]. Although indolent progress with a favorable long-term prognosis have been described before, about 20% of patients relapse or develop metastases, which can be fatal [3,5]. Former studies have mentioned many potential prognostic factors, including age, tumor stage, residual tumor, nuclear atypia, mitotic rate, and rupture of the tumor [2,8–12].

According to the National Comprehensive Cancer Network (NCCN) guidelines, version I 2017 [13], patients with stages II, III, or IV SCST should undergo comprehensive surgical staging as per epithelial ovarian cancer (EOC). For young patients with stage I SCST who desire preservation of fertility, fertility-sparing surgery seems to be the appropriate approach. Staging surgery includes hysterectomy, bilateral salpingo-oophorectomy, omentectomy, biopsy of peritoneum, and peritoneal washings. There is no consensus about the role of systematic lymphadenectomy [14,15].

There are several barriers to performing lymphadenectomy. Different from EOC, the incidence of lymph node metastasis in patients with SCST is extremely low. In addition, lymphadenectomy often requires an experienced gynecologist to perform it. Even so, the lymphadenectomy procedure causes lymphocysts developments, nerve and vessel injury, blood loss, and increased operating time [16]. Recently, much research has been inclined to suggest not to perform lymphadenectomy in patients with SCST, but it has not come to a consensus because of small groups of patients and different methodology [17–19]. To evaluate the prognostic significance of lymphadenectomy in malignant ovarian SCST, we performed a retrospective study of 72 cases in our institution and systematically reviewed all relevant published studies.

2. Materials and methods

We retrospectively reviewed the medical records of all patients who were diagnosed with malignant ovarian SCST and underwent primary surgery at Qilu Hospital of Shandong University (Shandong Province, China) between April 2005 and December 2016. Medical records were obtained from patients' admission and discharge files. Patients were excluded if they had concurrent malignancy disease. Data, including patient age, tumor histology, tumor size, tumor stage, surgery extent, and chemotherapy were reviewed. Tumor stage was according to International Federation of Gynecology and Obstetrics (FIGO) criteria version 2014 [20]. In this study, early stage was defined as stage I and II, and advanced stage was defined as stage III and IV. Conservative surgery was defined as unilateral salpingo-oophorectomy or cystectomy, and radical surgery was defined as hysterectomy and bilateral salpingo-oophorectomy orlymphadenectomy including pelvic and/or para-aortic lymph node dissection. Due to GCT accounts for most of the cases of SCST, patients with SCST and GCT were divided into lymphadenectomy and no lymphadenectomy group.

Our search proceeded using the terms, “sex cord stromal tumor” or “sex cord-gonadal stromal tumors” or “gynandroblastoma” or “lymphadenectomy” or “lymph node excision” or “lymph node dissection” with language limited to English. The terms were appropriately combined to search PubMed and Embase for publications as of July 20, 2017. The selected studies had to meet the following criteria: (1) the study investigated prognosis and lymphadenectomy in patients with malignant ovarian sex cord stromal tumor; (2) the diagnosis of malignant ovarian SCST were confirmed by a pathologist; (3) the odds ratio (OR), 95% confidence interval (95% CI), or the number of events used to calculate them were reported. Articles were excluded if they meet the following criteria: (1) case reports with fewer than 10 cases, (2) not providing enough information to estimate OR and 95% CI, (3) reporting duplicate or overlapping data. The Newcastle-Ottawa Scale (NOS) assessment was used to assess study selection, comparability, and outcome. A maximum of 9 points was assigned to each study: 4 for selection, 2 for comparability, and 3 for outcomes. A final score >6 was regarded as high quality [21]. Data extraction was conducted independently by two of the authors. All disagreements were settled by discussion with a third author.

Statistical analyses of significance of observed values were performed using Chi-Square. Kaplan-Meier survival analysis and Log Rank test were used to describe overall survival and difference between groups. Differences were considered significant when P values were found to be <0.05. All available ORs and 95% CIs were pooled using STATA statistical software version 19.0 (Stata Corp. LLC, College Station, TX, USA) to generate forest plots. Cochran Q test and I^2 statistics were used to evaluate heterogeneity. P value < 0.05 and/or I^2 > 50% showed potential heterogeneity existing among included studies. If so, a random-effects model was used. Otherwise, a fixed-effects model was used. The pathological type of GCT subgroup analysis was performed. Publication bias was evaluated by funnel plots. Sensitivity analysis was performed by omitting one study at a time to assess its effect on the final result.

3. Results

Between April 2005 and December 2016, 72 patients with malignant SCST were identified in our institution. The clinicopathologic characteristics are depicted in Table 1. The mean age of patients was 44.3 years (range, 8–80 years). Among the 72 patients, 69.4% had granulosa cell tumors (GCTs, $n = 50$), and 25% had Sertoli-Leydig cell tumors (SLCT, $n = 18$). In addition, 2.8% patients had steroid cell tumors ($n = 2$), and 2 patients each had sex cord tumor with annular tubules and SCST not otherwise specified. Of the 72 patients in this study, 88.9% ($n = 64$) were early stage (I–II), and 11.1% ($n = 8$) were advanced stage (III–IV)·Among the 72 patients, 47.2% ($n = 34$) underwent conservative surgery or radical surgery with lymphadenectomy, 28 of them were early stage, and 6 of them were advanced disease. In contrast 52.8% ($n = 38$) did not undergo lymphadenectomy. 36 of them were early stage, and 2 of them were advanced stage disease. None of lymph nodes were pathologically confirmed metastatic. The follow-up began with the primary surgery, and mean follow-up time was 56.1 months (range: 5 to 147 months). The 5- and 10-year overall survival rates were the same: 94.4% in SCST and 96.0% in GCT. No significant differences in the overall survival of patients with SCST or GCT were noted based on patient age, tumor size, surgery extent, nor administration of cytotoxic chemotherapy, except for tumor stage ($P = 0.01$ in SCTs and 0.029 in GCT, respectively). Lymphadenectomy showed no statistically

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