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Instructions for use

1 **Clinicopathological characteristics and prognostic factors of ovarian granulosa cell**

2 **tumors: A JSGO-JSOG joint study**

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39 **Abstract**

40 ***Objectives:*** The aim of this study was to elucidate the clinicopathological features of ovarian

41 granulosa cell tumors (GCTs) and to identify the prognostic factors.

42 ***Methods:*** The Japanese Society of Gynecologic Oncology (JSGO) conducted an

43 observational retrospective cohort study of women with GCTs enrolled in the Gynecological

44 Tumor Registry of the Japan Society of Obstetrics and Gynecology (JSOG) between 2002

45 and 2015. Clinicopathological features, including lymph node metastasis, were evaluated. In

46 addition, we performed a prognostic analysis of patients between 2002 and 2011 for whom

47 survival data were available. Kaplan–Meier and multivariate Cox proportional hazards

48 analyses were performed.

49 ***Results:*** We identified 1426 patients with GCT. Of the 222 patients who underwent lymph

50 node dissection, 10 (4.5%) had lymph node metastasis. The incidence of lymph node

51 metastasis in patients with pT1, pT2, and pT3 was 2.1%, 13.3%, and 26.7%, respectively

52 (p<0.001). Prognostic analysis was performed on 674 patients. In the multivariate Cox

53 regression analysis, residual disease after initial surgery (hazard ratio (HR)=10.39, 95%

54 confidence interval (CI)=3.15–34.29) and lymph node metastasis (HR=5.58, 95% CI=1.62–

55 19.19) were independent risk factors for cancer-specific survival.

56 ***Conclusions:*** In the initial surgery for GCTs, lymph node dissection can be omitted if the

57 operative finding is pT1. In cases of pT2 or higher, lymph node dissection should be

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58   considered. Debulking is critical for achieving no gross residual tumor at the end of the

59   surgery.

60   **Keywords:** lymph node metastasis; ovarian granulosa cell tumor; prognosis; surgery

61

62   **1. Introduction**

63   Granulosa cell tumors (GCTs) are tumors that constitute 2–5% of malignant ovarian

64   cancers [1]. These tumors are often characterized by later recurrences > 5 or 10 years after

65   initial treatment [2,3]. Because of their low incidence, many studies group combined GCTs

66   with other sex cord-stromal tumors (SLCTs) such as Sertoli-Leydig cell tumors in their

67   assessments [4–7]. It has been reported that 97% of these tumors have somatic mutations

68   in the *FOXL2* gene [8], elucidating the unique mutational profile of these tumors. For this

69   reason, it is important to conduct research that specifically targets GCTs.

70   However, there is a lack of robust evidence from clinical trials regarding the

71   treatment of GCTs. Because stage I cases account for 64% to 89% of all cases [9–11], the

72   primary treatment is mainly surgical. The purpose of surgery in the initial treatment of

73   ovarian cancer is to diagnose the histological type and extent of tumor involvement and to

74   remove the primary and metastatic lesions as much as possible. Despite the different

75   histological origin of the tumor, the surgical treatment strategy, including whether to perform

76   lymph node dissection, is in accordance with the guidelines for epithelial ovarian cancers.

4

77   Therefore, the primary objective of this study was to elucidate the clinicopathological

78   features of GCTs using bulky data from Japan's nationwide registry. The second objective

79   was to identify the prognostic factors for GCTs.

80

81   **2.   Materials and Methods**

82   ***2.1.   Data sources for the study***

83   This observational retrospective study used the Gynecologic Tumor Registry

84   database of the Japan Society of Obstetrics and Gynecology (JSOG), a nationwide project

85   undertaken by the Japanese Society of Gynecologic Oncology (JSGO). The dataset was

86   provided by the Gynecologic Oncology Committee of JSOG in 2018, and the study was a

87   collaboration between JSGO and JSOG. The JSOG database is an organ-based cancer

88   registry for gynecologic malignancies that records comprehensive information on cancer

89   types, properties of the tumor, therapeutic categories, and survival profile. The ovarian tumor

90   registry has been conducted annually by the Gynecologic Tumor Committee of JSOG since

91   2002. The registry comprises 466 hospitals, which account for approximately 50% of all new

92   cases with gynecologic malignancies in Japan. The JSGO database focuses on the leading

93   hospitals in Japan, such as university hospitals and cancer centers. The data in the present

94   study were mainly from surgeries and treatments performed by gynecologic oncologists

95   certified by the JSGO. Institutional review board approval was obtained from the Clinical

96   Research Committee of JSOG (2018-36-67) and the hosting institution, Tokai University

97   School of Medicine (17R-100).

98   **2.2.   Patients**

99   Histopathological classification codes (B11-00) were applied to specify the GCTs in

100   the database. Women with GCTs who underwent initial treatment between 2002 and 2015

101   were included in this study. Patients with unknown stage, those who had not undergone

102   surgery, and those who did not have an ovarian primary tumor were excluded. Among the

103   cases that met the inclusion criteria, patient age, FIGO stage, procedures in the initial

104   surgery (hysterectomy, salpingo-oophorectomy, and lymph node dissection), residual

105   disease after initial surgery (no gross residual disease, residual tumor diameter $\leq$1 cm,

106   diameter 1–2 cm, or >2 cm), neoadjuvant chemotherapy, and adjuvant chemotherapy were

107   extracted from the database. The recorded cancer stage was classified based on the 1988

108   International Federation of Gynecology and Obstetrics (FIGO). Surgical procedures were

109   registered as biopsy only, unilateral salpingo-oophorectomy, bilateral salpingo-

110   oophorectomy, salpingo-oophorectomy in conjunction with total hysterectomy, or tumor

111   removal from some other organ. In this registry, no distinction was made between unilateral

112   salpingo-oophorectomy and cystectomy (tumor resection). Similarly, we did not distinguish

113   between open and laparoscopic surgery in the registry. According to the findings of the

114   laparotomy and the histological findings of the removed specimen, each case was registered

115   using the pathological tumor node metastasis (pTNM) classification. In the JSOG

116   gynecologic tumor registry, the system is designed to register patients in the year of their

117   initial treatment and to provide prognostic reports three and five years later. At the time the

118   dataset was provided, survival information of the treated cases was included from 2002 to

119   2011. Survival outcomes were duration of follow-up, status of living, and cause of death.

120   Cancer-specific survival (CSS) was determined to be the period from diagnosis to death

121   caused by ovarian cancer. Cases without survival events or untraceable cases were

122   censored at the last visit with a known life condition.

123   **2.3.**   ***Statistical analyses***

124   Continuous variables are described as median and interquartile range (IQR). For

125   categorical variables, statistical differences were assessed using the chi-square test or

126   Fisher's exact test, as appropriate. The Kaplan–Meier method was used to form survival

127   curves, and the differences between the curves were assessed with the log-rank test. In

128   addition, the Cox proportional hazard regression model was used for multivariate analysis

129   using the step-down method with variables that were statistically significant in the univariate

130   analysis. The magnitude of statistical significance was expressed as hazard ratio (HR) and

131   95% confidence interval (CI). All statistical analyses were based on a two-sided hypothesis,

132   and statistical significance was set at $p < 0.05$. SPSS Statistics version 26 (IBM Corp.,

133   Armonk, NY, USA) was used for all analyses. The Strengthening the Reporting of

Observational Studies in Epidemiology (STROBE) guidelines were consulted to display the

results according to an observational cohort study [12].

3. Results

The patient selection schema is shown in Figure 1. There were 75,241 women with

ovarian malignancies documented in the JSOG Gynecologic Tumor Registry during the

study period. Granulosa cell histology was observed in 1,435 women. The final study

population comprised 1,426 (1.9%) women with ovarian GCTs.

3.1. Analysis of clinicopathological factors

The demographical and clinicopathological characteristics of the patients are

summarized in Table 1. The median (IQR) age was 55 (43–66) years. A total of 876 (61.4%)

patients were over 50 years of age. The majority of GCTs were classified as FIGO stage I

disease (89.1%). All the patients underwent surgical treatment. None of the GCT patients

received neoadjuvant chemotherapy. A total of 1,045 women (73.3%) underwent surgical

procedures including bilateral salpingo-oophorectomy and/or hysterectomy, whereas 339

(23.8%) underwent unilateral salpingo-oophorectomy or tumor resection. The rate of

complete gross resection in the initial surgery was 93.0%. A total of 222 patients (15.6%)

underwent lymph node dissection and 201 patients (14.2%) received adjuvant

chemotherapy. A higher stage (II–IV) was associated with more frequent adjuvant

8

153   chemotherapy use (9.0% chemotherapy use for stage I and 55.5% for stage II–IV, p<0.001).

154   Of the 222 patients who underwent lymph node dissection, 10 (4.5%) had

155   histologically confirmed lymph node metastasis. The rates of lymph node metastasis in

156   patients with pT1, pT2, and pT3 were 2.1%, 13.3%, and 26.7%, respectively (p<0.001).

157   There were no pT3a cases in which lymph node dissection was performed. These pT3

158   cases were either pT3b or pT3c (Table 2). The percentage of positive lymph nodes

159   associated with the extent of lymph node dissection was 5.0% (7/139 cases) in patients with

160   pelvic lymph node dissection only, 3.8% (3/79 cases) in patients with dissection of pelvic and

161   para-aortic lymph nodes, and 0% (0/4 cases) in patients with dissection of para-aortic lymph

162   nodes only.

163   *3.2.   Survival analysis*

164   We performed a survival analysis of 674 patients who were initially treated between

165   2002 and 2011 (Fig. 1). The median (IQR) follow-up time for the cohort was 51.0 (41.4–65.5)

166   months. Kaplan–Meier curves illustrate CSS (Fig. 2). CSS differed significantly according to

167   the FIGO stage (p<0.001), residual disease after initial surgery (p<0.001), and lymph node

168   status (p<0.001). The 5-year CSS rates for patients with FIGO stage I, II, III, and IV disease

169   were 98.2%, 89.3%, 81.0%, and 66.7%, respectively (Fig. 2-A). The 5-year CSS for patients

170   with no macroscopic residual disease, a residual disease diameter <1 cm, and residual

171   disease diameter >1 cm were 97.9%, 74.1%, and 33.3%, respectively (Fig. 2-B). The three

172	groups were compared for lymph node status. The 5-year CSS rates for patients negative for

173	metastasis, no node resection, and positive for metastasis were 97.4%, 96.9%, and 60.0%,

174	respectively (Fig. 2-C). In contrast, there was no significant CSS rate difference according to

175	age at diagnosis (<50 years vs. ≥ 50 years) (Supplementary Figure 1A), and lymph node

176	dissection (with vs. without) (Supplementary Figure 1B). In the multivariate Cox regression

177	analysis, residual disease after initial surgery (HR=10.39, 95% CI=3.15–34.29), and lymph

178	node metastasis (HR=5.58, 95% CI=1.62–19.19) were independent risk factors for CSS

179	(Table 3).

180	In addition, advanced cases of stage II and above (n=86) were examined. CSS

181	differed significantly according to residual disease after initial surgery (p<0.001)

182	(Supplementary Figure 2A). However, there was no difference in CSS between patients with

183	and without adjuvant chemotherapy (Supplementary Figure 2B). On the other hand, there

184	was no difference in CSS according to whether lymph node dissection was performed or not

185	in the examined patients with stage pT1 (Supplementary Figure 3).

186	Furthermore, when patients aged 18 to 49 years with a FIGO stage I GCTs (n=243)

187	were evaluated, the median (IQR) follow-up was 50.9 (41.1 to 65.6) months. There was no

188	difference in CSS between fertility-sparing surgical procedures (unilateral salpingo-

189	oophorectomy or tumor resection) and fertility-loss surgery including bilateral salpingo-

190	oophorectomy and/or hysterectomy (p=0.828) (Fig. 3).

191

4. Discussion

192

193   The present study is the second-largest cohort study of GCTs following the study

194   conducted by Seagle et al. [11]. Our study demonstrated that lymph node metastasis in

195   GCTs was positively associated with the macroscopic findings at laparotomy, and residual

196   tumor and lymph node metastasis at the initial surgery were poor prognostic factors.

197   Previous reports have shown that the incidence of lymph node metastasis in GCTs

198   is not very high. There are reports of 13 cases [13], 25 cases [14], and 36 cases [15] of

199   GCTs with lymph node dissection and no positive metastases. In another report, 34 cases [7]

200   and 47 cases of SCST were dissected without metastasis [5] and these papers concluded

201   that lymph node dissection can be omitted because positive node frequency is extremely

202   low. However, in a subsequent study with more patients, lymph node metastasis was found

203   in 3.1% (42/1350) [11] and 3.3% (19/572) [6]. In our study, the results were identical, with

204   metastasis observed in 4.2% (10/222). For the first time, we revealed that the incidence of

205   lymph node metastasis was positively associated with pT classification. For stage pT1

206   cases, lymph node dissection was performed in 192 (14.9%) cases, but metastasis was as

207   low as 2.1%. The combined metastatic rates of pT1 and pT2 remained low at 2.9%. This

208   was considerably lower than the 14.2% observed in FIGO stage I and II epithelial ovarian

209   cancer [16]. However, the incidence was higher in pT3 stage cases (26.7%), which was also

210   in accordance with previous reports of GCTs [11]. Therefore, based on the macroscopic

211   findings at the time of laparotomy, it may be possible to predict the risk of lymph node

212   metastasis. Seagle et al. [11] found that the non-dissected group had as poor a prognosis as

213   the metastasis-positive group. Conversely, in our study, the non-dissected group had the

214   same outcome as the node-negative group. This was probably due to the proportion of FIGO

215   stage I cases being much more common in our study compared to Seagle et al.'s [11] group.

216   Furthermore, analysis of pT1 cases only revealed that there was no difference in CSS

217   between patients with and without lymph node dissection.

218   The prognosis is poor for cases with a FIGO stage II [10,17] or III [18,19] and

219   patients over 50 years of age [19]; the existence of residual tumors and large tumor size are

220   also poor prognostic factors [9]. In cases of incomplete staging, recurrence is more frequent

221   [14]. In our study, the FIGO stage was a prognostic factor in the univariate analysis.

222   However, a multivariate analysis showed two selections: residual tumor at surgery and

223   histologically confirmed lymph node metastasis. Conversely, in stage I, which accounts for

224   most cases, the prognosis is poor in the IC stage [20,21], tumor rupture [3,20], incomplete

225   surgery [11], and non-staging surgery [21]. GCTs have been reported to have higher

226   genomic stability than epithelial ovarian cancers [22,23] and *FOXL2* mutations are highly

227   prevalent in both primary and metastatic lesions as well as in recurrent disease [24].

228   Therefore, Seagle et al. [11] proposed the possibility of de novo GCTs in the residual ovary

229 of some lesions that had been considered in late recurrence. According to a study of

230 metastatic sites, pelvic and intra-abdominal recurrences were more prevalent, with only

231 5.7% of recurrences in lymph nodes alone [25]. This information would help explore

232 therapeutic strategies.

233   The feasibility of fertility-sparing surgery has been reported as follows: Fertility-

234 sparing surgery is associated with no difference in disease-free survival for stage I GCT

235 patients under 50 years of age. In this study, fertility-sparing surgery is defined as the

236 preservation of the uterus and at least one ovary [26]. We also compared the surgical

237 procedures using the same definition and found no difference in CSS. However, Wang et al.

238 [26] cautioned that recurrence is more common in cases with incomplete staging in the

239 fertility-sparing group. In a study of stage I SCST in patients aged 18-49 years, fertility-

240 sparing surgery was carefully performed because of its inferiority for CSS, although there

241 was no difference in overall survival [27].

242 .   The strength of our study is that it was a nationwide survey and had the second-

243 largest sample size in the literature [11]. In this study, no ethnic information was requested at

244 the time of registration. However, since foreigners account for only 1.7% of Japan's

245 population, and most of them are from Asian countries, the JSOG data cover predominantly

246 Asian patients [28]. Therefore, this study can be considered the largest cohort study in Asia.

247 In addition, the JSGO database focuses on the leading hospitals in Japan, such as university

248   hospitals and cancer centers. The data in the present study were mainly from surgeries and

249   treatments performed by gynecologic oncologists. The present study had some limitations.

250   First, juvenile granulosa cell tumors were not registered separately, nor was there a

251   centralized pathology review. Second, for comprehensive surgical staging, there was no data

252   on each staging element (e.g., peritoneal washings, omentectomy, peritoneal biopsies)

253   because it is not a registry category. Third, data on the timing of relapse and the pattern of

254   recurrence have not been registered, so they are not available for investigation.

255   The following conclusions can be made based on the results of the present study:

256   At the time of the initial surgery, lymph node dissection can be omitted if the surgical findings

257   are pT1 after a thorough exploration of the abdominal cavity. In cases of pT2 or higher,

258   lymph node dissection should be considered. Debulking is also important to ensure that

259   there is no gross residual tumor at the end of the initial surgery. However, fertility-sparing

260   surgery may be considered in FIGO stage I cases, although even in these cases, staging

261   procedures such as inspection of the abdominal cavity and biopsy of the greater omentum

262   and peritoneum are required.

263

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265   None

266

270 **Conflict of Interests**

271 No potential conflict of interest relevant to this article was reported.

272

273 **Author contributions**

274   Study concept and design: YE and MM; acquisition of data: YE, WY, TT, MK, and

275 SN; analysis and interpretation of data: YE and MM; drafting of the manuscript: YE; Critical

276 revision of the manuscript for important intellectual content: YE, TE, and MM. Final approval

277 of manuscript: all authors.

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280 **References**

281 [1] S.T. Schumer, S.A. Cannistra, Granulosa cell tumor of the ovary, J. Clin. Oncol. 21(6)

282   (2003) 1180–1189. DOI: 10.1200/JCO.2003.10.019.

283 [2] Y.K. Lee, et al., Characteristics of recurrence in adult-type granulosa cell tumor, Int.

284   J. Gynecol. Cancer 18(4) (2008) 642–647. DOI: 10.1111/j.1525-1438.2007.01065.x.

285 [3] S. Bryk, et al., Characteristics and outcome of recurrence in molecularly defined

286   adult-type ovarian granulosa cell tumors, Gynecol. Oncol. 143(3) (2016) 571–577.

287   DOI: 10.1016/j.ygyno.2016.10.002.

288 [4] M. Zhang, et al., Prognostic factors responsible for survival in sex cord stromal

289   tumors of the ovary--an analysis of 376 women, Gynecol. Oncol. 104(2) (2007) 396–

290   400. DOI: 10.1016/j.ygyno.2006.08.032.

291 [5] M.M. Thrall, et al., Patterns of spread and recurrence of sex cord-stromal tumors of

292   the ovary, Gynecol. Oncol. 122(2) (2011) 242–245. DOI:

293   10.1016/j.ygyno.2011.03.020.

294 [6] D. Nasioudis, et al., Prevalence of lymph node metastasis and prognostic

295   significance of lymphadenectomy in apparent early-stage malignant ovarian sex

296   cord-stromal tumors, Gynecol. Oncol. 145(2) (2017) 243–247. DOI:

297   10.1016/j.ygyno.2017.03.005.

298 [7] H. Cheng, et al., Prognostic significance of lymphadenectomyin malignant ovarian

299   sex cord stromal tumor: A retrospective cohort study and meta-analysis, Gynecol.

300   Oncol. 148(1) (2018) 91–96. DOI: 10.1016/j.ygyno.2017.10.022.

301 [8] S.P. Shah, et al., Mutation of FOXL2 in granulosa-cell tumors of the ovary, N. Engl. J.

302   Med. 360(26) (2009) 2719–2729. DOI: 10.1056/NEJMoa0902542.

303 [9] H.D. Sun, et al., A long-term follow-up study of 176 cases with adult-type ovarian

304   granulosa cell tumors, Gynecol. Oncol. 124(2) (2012) 244–249. DOI:

305   10.1016/j.ygyno.2011.10.015.

306 [10] S. Bryk, et al., Clinical characteristics and survival of patients with an adult-type

307   ovarian granulosa cell tumor: a 56-year single-center experience, Int. J. Gynecol.

308   Cancer 25(1) (2015) 33–41. DOI: 10.1097/IGC.0000000000000304.

309 [11] B.L. Seagle, et al., Ovarian granulosa cell tumor: A National Cancer Database study,

310   Gynecol. Oncol. 146(2) (2017) 285–291. DOI: 10.1016/j.ygyno.2017.05.020.

311 [12] E. von Elm, et al., The Strengthening the Reporting of Observational Studies in

312   Epidemiology (STROBE) statement: guidelines for reporting observational studies,

313   Lancet 370(9596) (2007) 1453–1457. DOI: 10.1016/S0140-6736(07)61602-X.

314 [13] Abu-Rustum, N. R., Retroperitoneal nodal metastasis in primary and recurrent

315   granulosa cell tumors of the ovary, Gynecol. Oncol. 103(1)(2006) 31–34.

316 [14] J.Y. Park, et al., Surgical staging and adjuvant chemotherapy in the management of

317   patients with adult granulosa cell tumors of the ovary, Gynecol. Oncol. 125(1) (2012)

318   80–86. DOI: 10.1016/j.ygyno.2011.12.442.

319   [15]   J. Brown, et al., Patterns of metastasis in sex cord-stromal tumors of the ovary: can

320   routine staging lymphadenectomy be omitted?, Gynecol. Oncol. 113(1) (2009) 86–90.

321   DOI: 10.1016/j.ygyno.2008.12.007.

322   [16]   M. Kleppe, et al., Lymph node metastasis in stages I and II ovarian cancer: a review,

323   Gynecol. Oncol. 123(3) (2011) 610–614. DOI: 10.1016/j.ygyno.2011.09.013.

324   [17]   S. Erkılınç, et al., Does lymphadenectomy effect postoperative surgical morbidity and

325   survival in patients with adult granulosa cell tumor of ovary?, J. Obstet. Gynaecol.

326   Res. 45 (2019) 1019–1025. DOI: 10.1111/jog.13928.

327   [18]   K. Uygun, et al., Granulosa cell tumor of the ovary: retrospective analysis of 45

328   cases, Am. J. Clin. Oncol. 26(5) (2003) 517–521. DOI:

329   10.1097/01.coc.0000037918.88451.6A.

330   [19]   G. Mangili, et al., Long-term follow-up is crucial after treatment for granulosa cell

331   tumours of the ovary, Br. J. Cancer 109(1) (2013) 29–34. DOI: 10.1038/bjc.2013.241.

332   [20]   M.K. Wilson, et al., Stage I granulosa cell tumours: A management conundrum?

333   Results of long-term follow up, Gynecol. Oncol. 138(2) (2015) 285–291. DOI:

334   10.1016/j.ygyno.2015.05.011.

335   [21]   D. Wang, et al., Clinicopathological characteristics and prognosis of adult ovarian

336   granulosa cell tumor: a single-institution experience in China, Onco Targets Ther. 11

337   (2018) 1315–1322. DOI: 10.2147/OTT.S155473.

338   [22]   D. Mayr, et al., Analysis of selected oncogenes (AKT1, FOS, BCL2L2, TGFbeta) on

339   chromosome 14 in granulosa cell tumors (GCTs): a comprehensive study on 30

340   GCTs combining comparative genomic hybridization (CGH) and fluorescence-*in situ*-

341   hybridization (FISH)*,* Pathol. Res. Pract. 204(11) (2008) 823–830. DOI:

342   10.1016/j.prp.2008.07.009.

343   [23]   J.A. Fletcher, et al., Ovarian granulosa-stromal cell tumors are characterized by

344   trisomy 12*,* Am. J. Pathol. 138(3) (1991) 515–520.

345   [24]   G.F. Zannoni, et al., FOXL2 molecular status in adult granulosa cell tumors of the

346   ovary: A study of primary and metastatic cases*,* Oncol. Lett. 12(2) (2016) 1159–1163.

347   DOI: 10.3892/ol.2016.4711.

348   [25]   G. Mangili, et al., Recurrent *granulosa* cell tumors (GCTs) of the ovary: a MITO-9

349   retrospective study*,* Gynecol. Oncol. 130(1) (2013) 38–42. DOI:

350   10.1016/j.ygyno.2013.04.047.

351   [26]   D. Wang, et al., Analysis of oncologic and reproductive outcomes after fertility-

352   sparing surgery in apparent stage I adult ovarian granulosa cell tumors*,* Gynecol.

353   Oncol. 151(2) (2018) 275–281. DOI: 10.1016/j.ygyno.2018.09.004.

354   [27]   D. Nasioudis, et al., Safety of fertility-sparing surgery for premenopausal women with

355   sex cord-stromal tumors confined to the ovary*,* Int. J. Gynecol. Cancer 27(9) (2017)

356   1826–1832. DOI: 10.1097/IGC.0000000000001110.

357   [28]   https://www.soumu.go.jp/main_sosiki/jichi_gyousei/c-

358   gyousei/zairyu_1/pdf/080630_1_si1.pdf. accessed date: 26 May 2021.

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361

362   **Figure Captions**

363   **Fig. 1** Flow chart of the patients included in the study

364   JSOG, Japan Society of Obstetrics and Gynecology

365

366   **Fig. 2** Cancer-specific survival of patients with granulosa cell tumors by (A) FIGO stage, (B)

367   residual disease after initial surgery, and (C) lymph node states

368   FIGO, International Federation of Gynecology and Obstetrics

369

370   **Fig. 3** Cancer-specific survival of women aged 18 to 49 years with FIGO stage I granulosa

371   cell tumors by surgical procedure

372   BSO, bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy

373

374   **Supplementary Fig. 1** Cancer-specific survival of patients with granulosa cell tumors by (A)

375   age at diagnosis and (B) lymph node dissection.

376

377   **Supplementary Fig. 2** Cancer-specific survival of patients with advanced (stage II-IV)

378   granulosa cell tumors by (A) residual disease after initial surgery and (B) adjuvant

379   chemotherapy.

380

381   **Supplementary Fig. 3** Cancer-specific survival of patients with pT1 granulosa cell tumors by
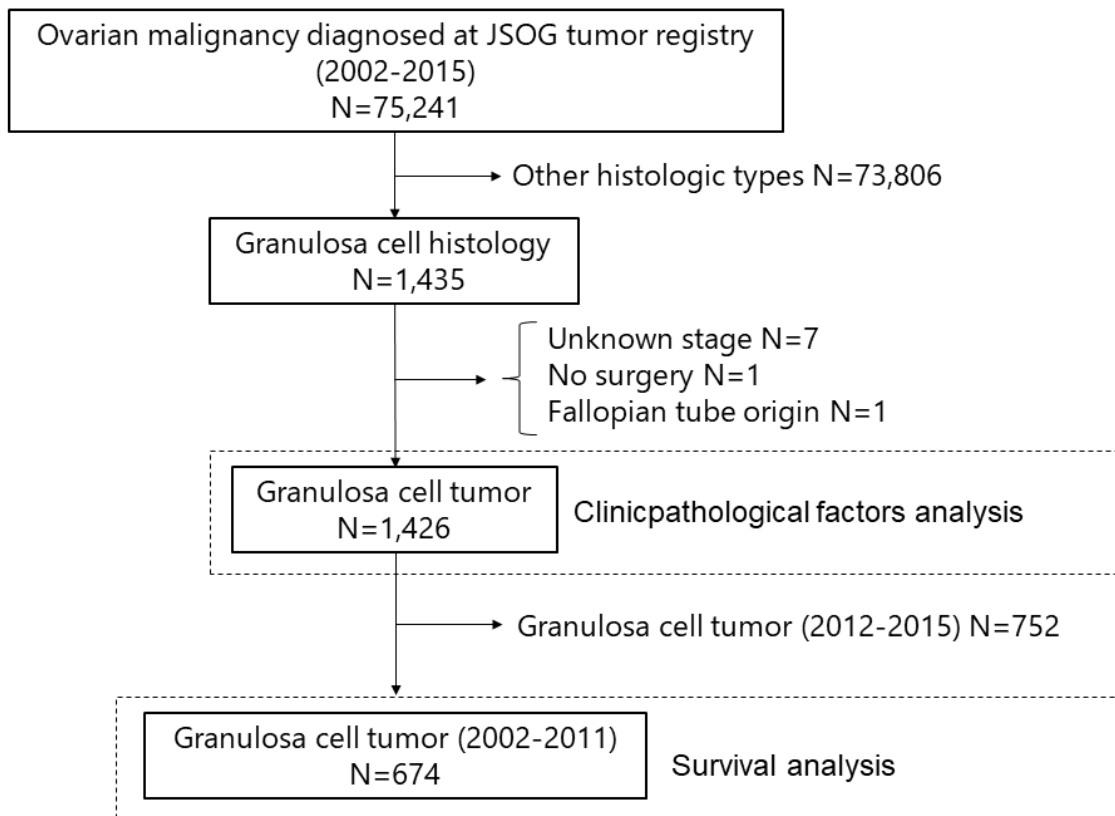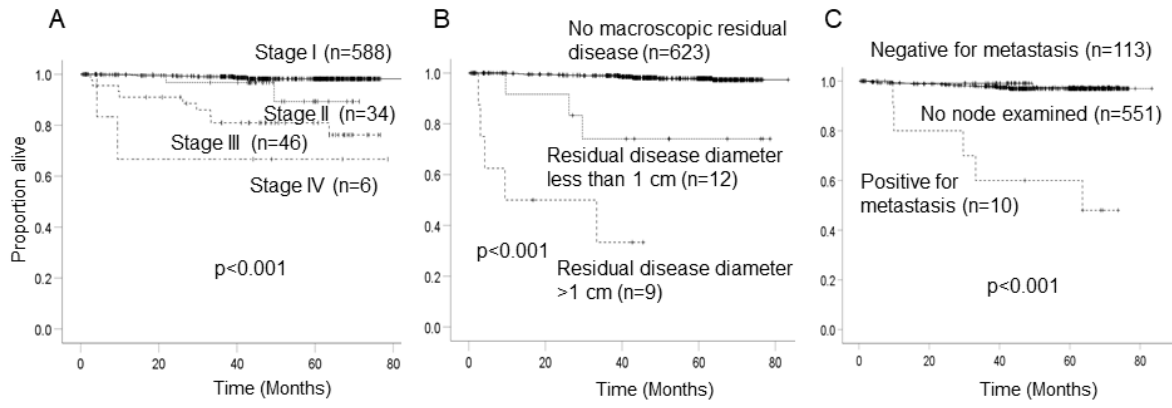
382   lymphadenectomy.

383

Fig. 1


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┌─────────────────────────────────────────────┐
│ Ovarian malignancy diagnosed at JSOG tumor registry │
│                    (2002-2015)                │
│                    N=75,241                   │
└─────────────────────────────────────────────┘
                      │
                      ├──────────→ Other histologic types N=73,806
                      ▼
        ┌──────────────────────────┐
        │ Granulosa cell histology │
        │         N=1,435          │
        └──────────────────────────┘
                      │
                      │              ┌ Unknown stage N=7
                      ├──────────→ ┤  No surgery N=1
                      │              └ Fallopian tube origin N=1
                      ▼
        ┌──────────────────────────┐
        │ Granulosa cell tumor     │   Clinicpathological factors analysis
        │      N=1,426             │
        └──────────────────────────┘
                      │
                      ├──────────→ Granulosa cell tumor (2012-2015) N=752
                      ▼
        ┌──────────────────────────┐
        │ Granulosa cell tumor (2002-2011) │   Survival analysis
        │           N=674          │
        └──────────────────────────┘
```

Fig. 2

A

Proportion alive

Stage I (n=588)

Stage II (n=34)

Stage III (n=46)

Stage IV (n=6)

p<0.001

Time (Months)

B

No macroscopic residual
disease (n=623)

Residual disease diameter
less than 1 cm (n=12)

p<0.001

Residual disease diameter
>1 cm (n=9)

Time (Months)

C

Negative for metastasis (n=113)

No node examined (n=551)

Positive for
metastasis (n=10)

p<0.001

Time (Months)

24

Fig. 3

A

B

A

B

27

Table 1 Demographic and clinicopathological characteristics of patients with granulosa cell tumor

Age (years)		
<40	244	(17.1%)
40-49	306	(21.5%)
50-59	319	(22.4%)
60-69	310	(21.7%)
70≦	247	(17.3%)
Stage (FIGO 1988)		
I	1,271	(89.1%)
IA	919	
IB	13	
IC	339	
II	66	(4.6%)
IIA	6	
IIB	19	
IIC	41	
III	79	(5.5%)
IIIA	7	
IIIB	18	
IIIC	54	
IV	10	(0.7%)
IVA	2	
IVB	8	
Operative procedure		
USO or tumor resection	339	(23.8%)
BSO or/and hysterectomy	1,045	(73.3%)
Other	42	(2.9%)
Lymph node dissection		
Yes	222	(15.6%)
Pelvic	139	
Pelvic and paraaortic	79	
Paraaortic	4	
No	1,204	(84.4%)
Residual disease after initial surgery		
No	1,326	(93.0%)
Yes	44	(3.1%)

residual tumor diameter ≤1 cm	25	
residual tumor diameter 1–2 cm	4	
residual tumor diameter >2 cm	15	
Not reported	56	(3.9%)
Adjuvant chemotherapy		
Yes	201	(14.2%)
No	1,225	(85.8%)

USO, unilateral salpingo-oophorectomy; BSO, bilateral salpingo-oophorectomy

Table 2 Lymph node metastasis rate by pTNM classification

pTNM classification	Number of cases of lymph node dissection		Number of histologically diagnosed metastasis-positive cases		Rate of metastasis	
pT1	192		4		2.1% *	
pT1a		121		2		1.7%
pT1b		3		0		0.0%
pT1c		68		2		2.9%
pT2	15		2		13.3% *	
pT2a		1		0		0.0%
pT2b		5		0		0.0%
pT2c		9		2		22.2%
pT3	15		4		26.7% *	
pT3a		0		-		-
pT3b		5		1		20.0%
pT3c		10		3		30.0%
total	222		10		4.5%	

 * p<0.001

pTNM, pathological tumor node metastasis

Table 3 Risk factors for cancer-specific survival of patients with granulosa cell tumor

Factors	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
FIGO stage		<0.001		0.082
I	1		1	
II-IV	10.74 (4.59-25.14)		3.12 (0.87-11.23)	
Residual disease after initial surgery		<0.001		<0.001
No macroscopic residual disease	1		1	
Positive	29.40 (11.57-69.71)		10.39 (3.15-34.29)	
Lymph node metastasis		<0.001		0.006
Negative or not examined	1		1	
Positive	21.15 (7.78-57.50)		5.58 (1.62-19.19)	

HR, hazard ratio; CI, confidence interval FIGO, International Federation of Gynecology and Obstetrics.