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Symptoms of Women With High-Risk, Early-Stage Ovarian Cancer

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Abstract

Objective: To assess the presentation, characteristics, and prognostic significance of symptoms in patients with high-risk early stage epithelial ovarian cancer.

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A list of Gynecologic Oncology Group member institutions who participated in the primary treatment studies can be found in Appendix 1.

Methods: A retrospective chart review was performed on all patients enrolled in a phase III clinical trial (GOG 157). All patients had surgically staged, high-risk, early stage epithelial ovarian cancer (stage IA/IB and grade 3, any clear cell, stage IC or II). Chi-square and Kaplan-Meier estimates and Cox proportional hazards models were used for statistical analyses.

Results: Of 419 patients evaluated for symptoms, 301 (72%) presented with one or more symptoms and 118 (28%) were asymptomatic but had a mass found on examination. Forty percent had only one and 32% more than one symptom. In those with at least one symptom, the most common were abdominal and pelvic pain (31%) and increased girth or fullness (26%). Overall, 23%, 27%, and 46% of patients with tumors ≤10 cm, >10–15 cm, and >15 cm, respectively, had multiple symptoms ($p<0.001$). There was no significant difference in presentation of symptoms based on age, stage, or histologic subtype. Symptoms at diagnosis were not associated with recurrence or survival.

Conclusion: Over 70% of patients with high-risk, early stage, epithelial ovarian cancer present with one or more symptoms, with the most common being abdominal or pelvic pain. The proportion of women with symptoms and the number of symptoms increase with enlarging tumor size.

PRÉCIS

Over 70% of patients with high-risk early stage ovarian cancer present with symptoms, most commonly abdominal or pelvic pain.

INTRODUCTION

Ovarian cancer is the most lethal of all gynecologic pelvic malignancies in the United States, resulting in over 13,940 deaths annually.[1] The majority are diagnosed at an advanced stage and most will develop recurrent and subsequently chemo-resistant disease.[2] The ability to identify patients with early stage cancer may influence their overall survival (OS).

Even though most ovarian cancer patients present with symptoms, the majority are non-specific and reported in those with advanced disease.[3–10] In a national survey of women with ovarian cancer, Goff and colleagues reported that 95% of women reported symptoms prior to their ovarian cancer diagnosis.[4] Therefore, the use of symptom awareness as an educational tool to identify ovarian cancer in earlier stage of disease has received significant attention.[11] However, since the majority of ovarian cancer patients are diagnosed at advanced stages, prior studies that have assessed symptoms were on patients with advanced stage disease.[7–10, 16]

Thus, we performed this secondary analysis on over 400 patients with early stage high-risk ovarian cancer to evaluate the presentation and characteristic symptoms of early stage ovarian cancer, and to attempt to identify the relationship between these symptoms with respect to clinico-pathologic characteristics and prognosis in early stage disease.

METHODS

We undertook a retrospective review of all charts from patients enrolled on GOG protocol 157, a randomized phase III trial of surgically staged FIGO stage IA grade 3, IB grade 3, any (stage I or II) clear cell, IC, and stage II epithelial ovarian cancer patients.[17] Women were randomized to either three or six cycles of chemotherapy consisting of paclitaxel (175 mg/m^2) and carboplatin (AUC 7.5) every 21 days.

Of 427 patients with high-risk early stage ovarian cancer, 419 (98%) had available data from chart review regarding symptoms or were noted to be asymptomatic but presented with a mass found on routine examination. This group of 419 patients formed the cohort of our study. Recurrence-free survival (RFS) and overall survival (OS) were evaluated in relation to presenting symptom(s). RFS was measured from the date of study enrollment until clinical progression or death, whichever came first. OS was defined as the time interval from study entry until death.

A Cochran-Mantel-Haenszel Chi-square (mean score statistic) test was used to compare the presentation of symptoms (no symptom, single symptom and multiple symptoms) by age, stage, histologic subtype or tumor size. A Cox proportional hazards model was used to examine the association between presenting symptoms and RFS and OS. Kaplan-Meier survival plots based on presenting symptoms were calculated and compared using the log rank test. A p-value <0.05 was considered statistically significant. The study was approved by the Institutional Review Board of all participating NRG/GOG institutions.

RESULTS

Of the 419 patients evaluated for symptoms, 301 (72%) presented with one or more symptoms and 118 (28%) were asymptomatic with a mass found on physical examination. A total of167 (40%) had only one symptom and 134 (32%) had multiple symptoms (Table 1, Figure 1).

There was a significant association between primary tumor size and the percentage of patients experiencing symptoms1, with 65%, 71%, and 79% of those with tumors ≤10 cm, 11–15 cm, and >15 cm, having at least one symptom, respectively (Table 2, Figure 2).

Symptoms were not significantly associated with age, stage, or histologic subtype (Table 2). There was no association between presence of symptoms (single or multiple) and risk of recurrence or survival (Figures 3a and 3b). In figure 4, we compared the characteristic symptoms of early stage cancer patients using our data to those with advanced stage disease based on a historical cohort.[4]

Discussion

Since the presenting symptoms of advanced stage ovarian cancer are believed to be non-specific, this cancer has been previously termed the “silent disease.”[18] Given that most women are diagnosed in later stages, prior studies on assessing symptoms were based predominately on advanced stage patients.[4,5,7–9,16,18,19] Compared to women without

ovarian cancer, most ovarian cancer patients present with one or more non-specific symptoms of abdominal pain, bloating, difficulty eating or all three.[6 18] (Box 1)Likewise, we found that over 70% of our patients presented with one or more symptoms and the most common was abdominal or pelvic pain.

One of these five common symptoms identified in this current report can potentially be used to evaluate patients for early stage ovarian cancer. Based on a comprehensive literature review, Jayde et al found that nearly 95% of ovarian cancer patients were symptomatic.[20] The lower percentage of symptomatic patients in our study may be due to the fact that all 419 patients had early stage as opposed to advanced stage disease.

It is unclear whether the characteristic symptoms of those with early stage disease differ from that of advanced stage. Prior studies have described the symptoms of advanced cancers as anorexia, early satiety, and abdominal distention related to metastatic involvement of extra-pelvic disease. In contrast, symptoms of early stage disease may be more related to pelvic involvement with associated with lower abdominal-pelvic symptoms.[7] In this current report, we also showed that the predominant symptoms were located in the pelvic region including pelvic pain, pelvic pressure, and urinary symptoms. We then compared the rates of these symptoms to that of advanced cancers using a historical report from Goff et al and showed that fullness and abdominal girth and gastrointestinal symptoms appeared to be much higher in advanced compared to early stage disease.[4] (Figure 4) Others have also demonstrated that early stage cancer patients have symptoms but with less frequency compared to those with late stage disease.[21]

In our series, we found a significant correlation between primary tumor size and the percentage of patients experiencing symptoms. (Figure 2). Goff and colleagues used an index of multiple symptoms combined with frequency (>12 times per month) and time interval to help clinicians better assess ovarian cancer symptoms.[5] In addition, a meta-analysis found that ovarian cancer patients had a triad of symptoms depicted as: increased abdominal size, bloating and urinary urgency at 44% compared to only 8% in primary care patients without cancer.[21] Although the use of a symptom index may help evaluate early symptoms of ovarian cancer, it has not been recommended for routine use.[22,23,24]

Our study did not find an association between symptoms and survival (Figures 3a and 3b). In contrast, other studies have found correlations between multiple symptoms at diagnosis such as lower extremity edema to poorer survival.[25].[26] DiSilvestro and colleagues found an association between the severity of symptom and an increased risk of death.[27] Similarly, the Diagnosing Ovarian Cancer early (DOvE) study investigators revealed that open-access assessment of ovarian cancer symptoms may lead to earlier diagnosis and better prognosis.[28]

Our patients underwent staging surgery by gynecologic oncologists and all tumor underwent central pathology review. However, it is noteworthy that our data were extracted from the history and physical report during clinical trial enrollment and lacks information on body mass index, comorbidities, current medications past gynecologic, uro-gynecologic and surgical history, and the initial disease presentation at primary care. A prior study did show that an interview or questionnaire can result a higher rate of reported symptoms

compared to medical records extraction alone.[21] Moreover, our retrospective data were not standardized and had missing information frequency, duration and intensity of symptoms with potential recall bias. Nevertheless, prospective studies can be designed by using the five most commons symptoms found in this study to further validate previously published questionnaires.[29]

Additional research is warranted to evaluate symptom awareness in early stage cancers and possibly incorporating novel serum biomarkers and wearable monitoring devices.[30,31] As one of the few studies that describe symptoms of early-stage high risk ovarian cancer, our data showed that over 70% of patients present with one or more symptoms, with the most common being abdominal or pelvic pain. Thus, even in early stage disease, ovarian cancer is not necessarily a “silent disease”.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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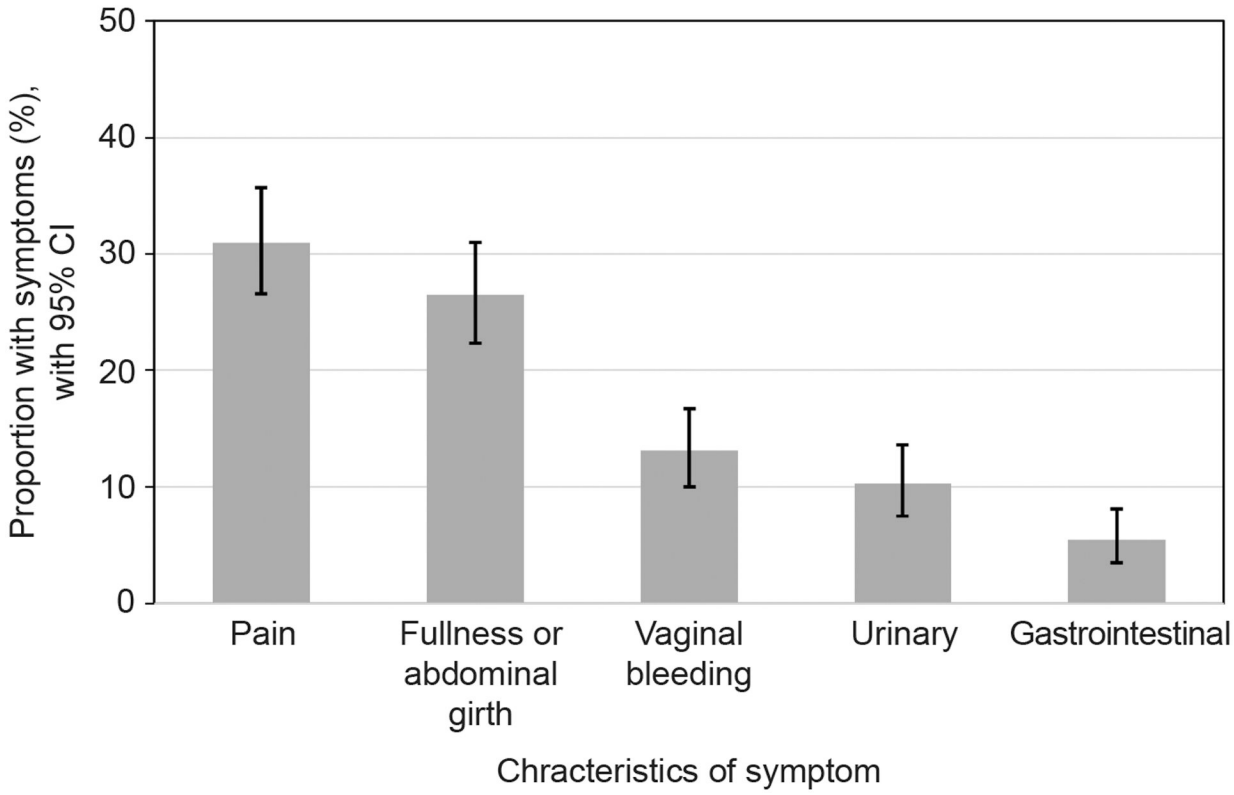

Figure 1:
Characteristics of symptoms associated with early-stage high-risk ovarian cancer patients

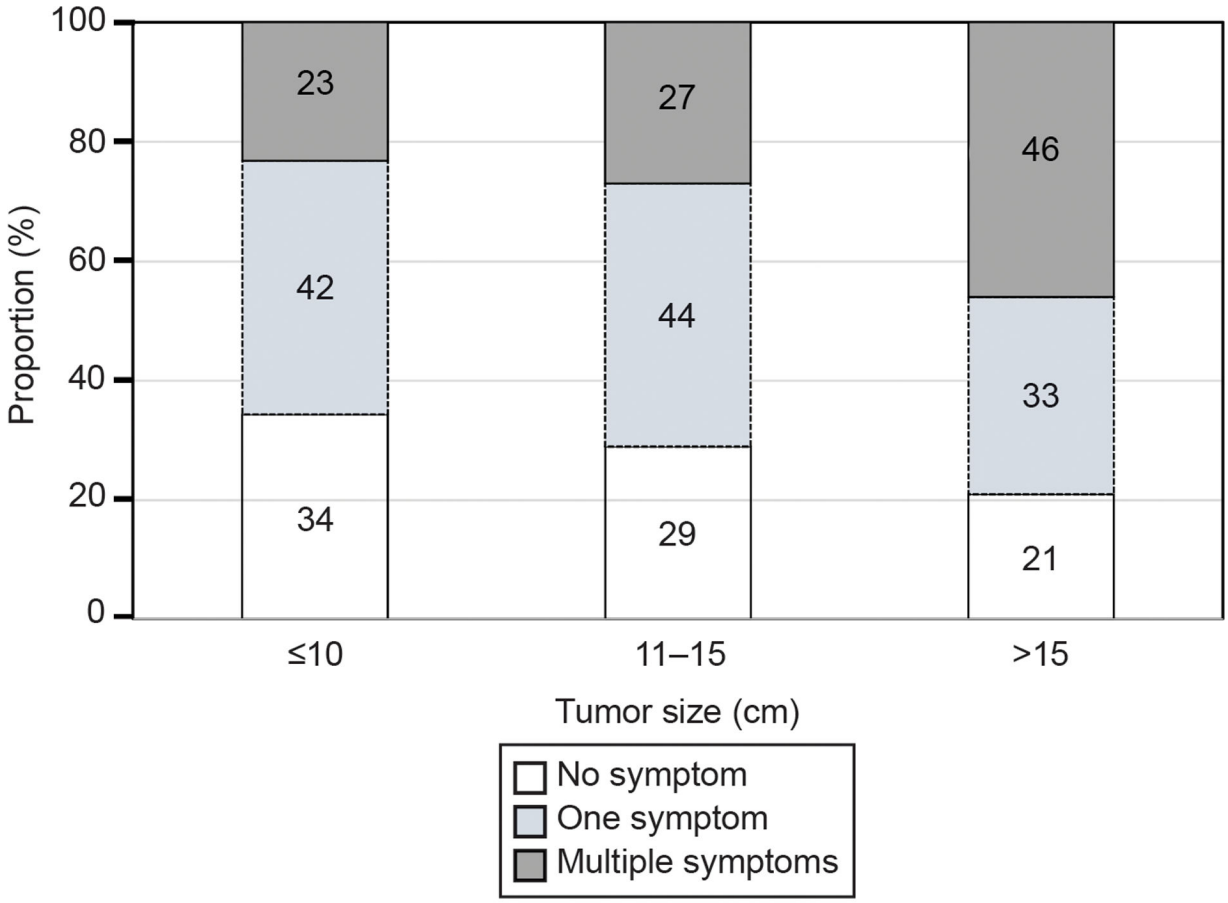

Figure 2:
Presentation of symptoms based on tumor size.

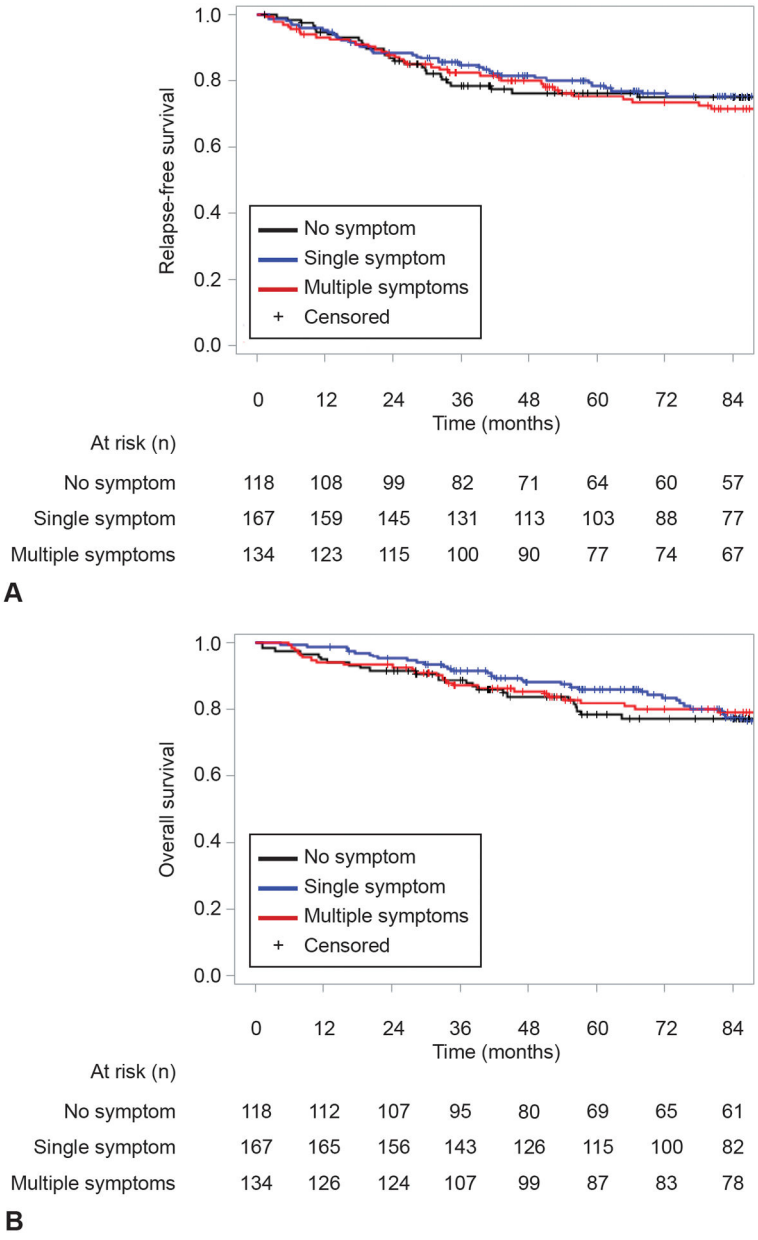

Figure 3:

A. Relapse-free survival based on symptoms (log-rank test *P*=.712). **B.** Overall survival based on symptoms (log-rank test *P*=.917).

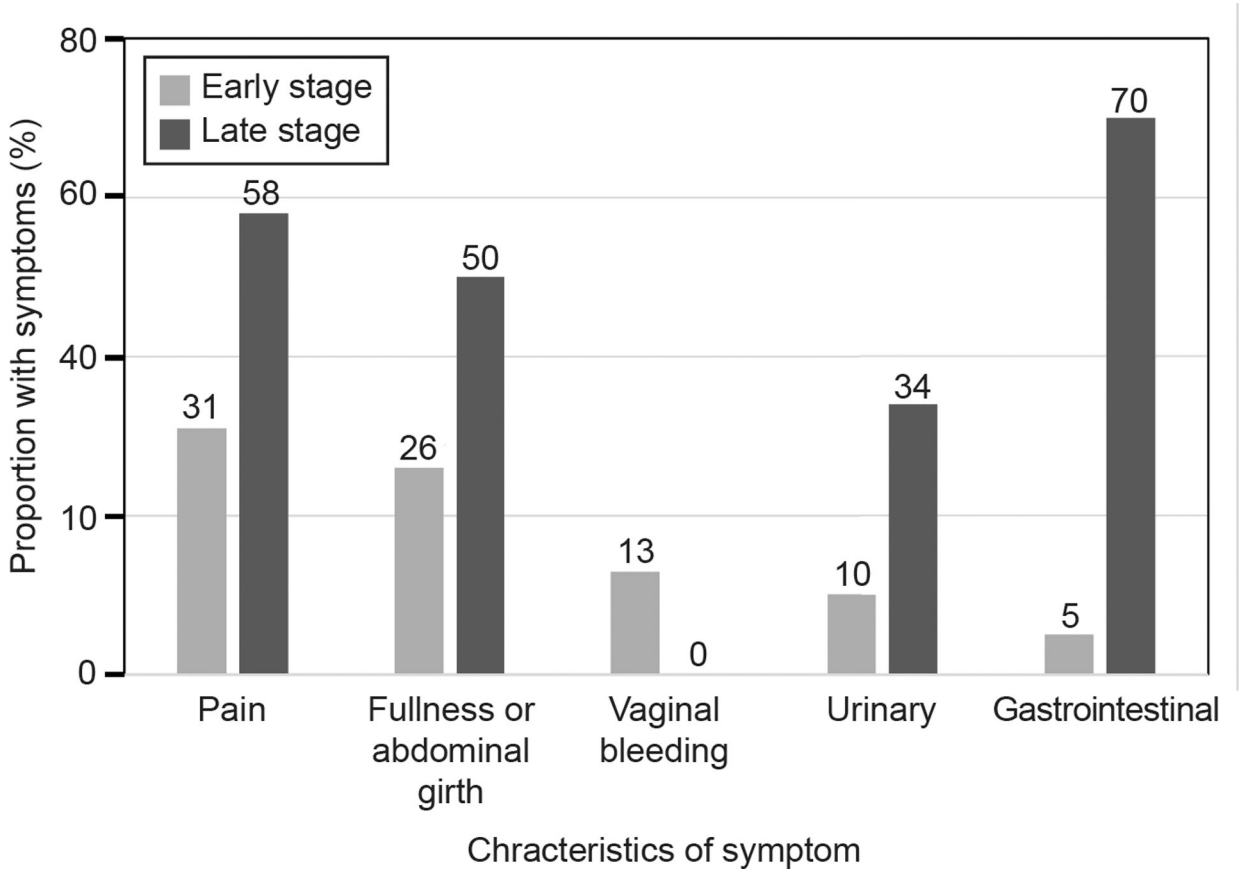

Figure 4:
Ovarian cancer symptoms: early versus advanced stage. Data from early-stage cancer based on current report and data from advanced-stage disease from historical report.[4]

Table 1.

Presentation of Symptoms for Patients with Early-Stage High Risk Ovarian Cancer at Time of Diagnosis (N=419)

	No. Patients	Distribution (%)	95% CI (%)
Number of symptoms *			
0 (no symptom)	118	28	23 – 34
1 (one symptom)	167	40	35 – 45
>1 (multiple symptoms)	134	32	27 – 37
Symptom description **			
Pain (abdominal or pelvic)	130	31	27 – 36
Fullness / increased abdominal girth	111	27	22 – 31
Abnormal vaginal bleeding	55	13	10 – 17
Urinary	43	10	8 – 14
Gastro-intestinal	23	6	4 – 8

* Simultaneous 95% confidence interval (CI) for the multinomial distribution calculated according to the method proposed by Sison and Glaz.

** *Indicating the proportion with each symptom among total of 419 patients. Some patients presented more than one symptom. 95% confidence interval (CI) calculated based on* Clopper-Pearson *exact method.*

Table 2.

Presentation of Symptoms by Demographic and Clinico-pathologic Characteristics in Patients With Early-Stage, High-Risk Ovarian Cancer

	No Symptoms	**Single Symptom**	**Multiple Symptoms**	***P* value**[1]
	No. (%)	No. (%)	No. (%)	
Age (years)				0.889
< 60	73 (28%)	203 (40%)	84 (32%)	
≥ 60	45 (28%)	64 (40%)	50 (31%)	
Stage				0.267
IA/IB	24 (31%)	32 (41%)	22 (28%)	
IC	55 (26%)	81 (38%)	76 (36%)	
II	39 (30%)	54 (42%)	36 (28%)	
Histology				0.979
Serous	27 (28%)	41 (43%)	27 (28%)	
Endometrioid	29 (28%)	41 (40%)	33 (32%)	
Clear cell	36 (28%)	50 (39%)	41 (32%)	
Mucinous	9 (29%)	11 (35%)	11 (35%)	
Other	17 (27%)	24 (38%)	22 (35%)	
Tumor Size (cm) *				<0.001
≤ 10	44 (34%)	54 (42%)	30 (23%)	
11 – 15	44 (29%)	68 (44%)	42 (27%)	
> 15	29 (21%)	44 (33%)	62 (46%)	

[1] Cochran-Mantel-Haenszel Chi-square (mean score statistic) test used to compare the distributions.

* Of all patients with information on tumor size (n=417). Pairwise comparison: p=0.284 for tumor size 11–15 cm vs. ≤10 cm; p<0.001 for tumor size >15 cm vs. ≤10 cm; p=0.005 for tumor size >15 cm vs. ≤11–15 cm.