RESEARCH ARTICLE

Risk Factors for Appendiceal Metastasis with Epithelial Ovarian Cancer

Mahmut Kuntay Kokanali*, Ali Irfan Guzel, Selcuk Erkilinc, Aytekin Tokmak, Hasan Onur Topcu, Tayfun Gungor

Abstract

Purpose: To investigate the risk factors for appendiceal metastasis of epithelial ovarian cancer and compare findings with the previous studies. Materials and Methods: One hundred and thirty-four patients with epithelial ovarian cancer were assessed in this study. All of them had undergone a surgical procedure including appendectomy. Of these, 21 (15.7%) patients who had appendiceal metastasis were analyzed as the case group and the patients with no metastasis were the controls, compared according to stage, grade, histology of tumor, preoperative Ca125 levels, presence of ascites, peritoneal cytology, diameter and site of tumor considered as risk factors. Results: We found statistically significant differences between the groups in terms of stage, grade, right-sided tumor location, presence of ascites, diameter of tumor≥10 cm and positive peritoneal cytology ($p<0.05$). In the logistic regression model, stage, grade, presence of ascites, right-sided location and diameter of tumor were independent risk factors. ROC curve analysis showed that stage, grade and diameter of the tumor were discriminative factors for appendiceal metastasis. Conclusions: In epithelial ovarian cancer, stage, grade, presence of ascites, right-sided location and large tumor size have importance for estimation of risk of appendiceal metastasis. As we compare our findings with previous studies, there is no definite recommendation for the risk factors of appendiceal metastasis in epithelial ovarian cancer and more studies are needed.

Keywords: Appendix - metastasis - epithelial ovarian cancer

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Introduction

Ovarian cancer is the eighth most cancer type of cancer and the seventh most common cause of cancer-related death among women worldwide (Jemal et al., 2011). In a study designed by Wang et al. (2014), the rate of ovarian cancer was reported as 7.91/100,000 (person-years) and the age-adjusted rate was 5.35/100,000 (person-years) between 1999-2010. Appendectomy is advocated in epithalial ovarian cancer such as; borderline, serous and mucinous epithelial ovarian cancers with metastatic cancers of suspicious gastrointestinal origin (Timofeev et al., 2010). The importance of appendectomy in patients subjected to laparotomy in early stage ovarian cancers remains as a controversial topic (Feigenberg et al., 2013).

Previous studies have accepted that routine removal of appendix should be performed in all patients who undergo surgery for staging and cytoreduction of ovarian cancer. And they also claimed that removal of the appendix leads to upstaging of disease, prevention of acute appendicitis, more accurate diagnosis (including ruling out primary appendiceal disease), and decreased risk of future surgical complications from extensive adhesions (Ayhan et al., 2005; Lin et al., 2013). However, Malfetano (1987) has recommended to leave the appendix in patients with early-stage disease because of their low risk of appendiceal metastasis. Gaemmaghami et al. (2011) evaluated the effect of debulking surgery without appendectomy on survival rates in ovarian cancer and found that appropriate surgery appears to be an important point for optimal survival. In current study, we therefore aimed to investigate the risk factors of appendiceal metastasis in epithelial ovarian cancers and compare our findings with the literature.

Materials and Methods

In this retrospective study, we enrolled a total of one hundred and thirty four women who underwent a comprehensive surgical staging procedure (including; total abdominal hysterectomy, bilateral salpingo-oopherectomy, peritoneal washing, bilateral pelvic and para-aortic lyphadenectomy, infracolic omentectomy and appendectomy) for primary epithelial ovarian cancer over a period of 2 years; at Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara/Turkey, that is a tertiary research hospital in centre of Turkey. All patients had abnormal pelvic findings on imaging,

*Women's Health Education and Research Hospital, Ankara, Turkey *For correspondence: k.kokanal@yahoo.com.tr*

necessitating surgery by a gynecologic oncologist. Demographic and clinicopathologic data were collected from hospital charts including patient's age, parity, and family history of ovarian or breast cancer, preoperative Ca125 levels, intraoperative findings, final histopathologic diagnosis and stage of disease according to International Federation of Gynecology and Obstetrics (FIGO). Tumor grade, size, site, presence or absence of ascite and positive peritoneal cytology, lymph node, omentum and appendix involvement were also recorded. Surgical staging procedure was performed by the same surgical team in all of the cases and all of the paraffin blocks were reviewed by a single pathologist. Patients with a previous history of cancer, concomitant tumors, primary appendiceal cancer, primary gastrointestinal malignancy with metastasis to the appendix, appendectomy as part of secondary tumor-reductive surgery, incomplete clinicopathologic data, primary surgery for ovarian cancer not performed at our hospital were excluded from the study. Twenty one patients with microscopic or gross appendiceal metastasis had been selected as case group, and one hundred and thirteen patients with no appendiceal metastasis had been selected as controls. Approval was not obtained from the instutional review board because of the retrospective design of the study.

Statistics

Mean and standard deviation (SD) were calculated for continuous variables. The normality of the variables was analyzed by Kolmogornov Smirnov test. Chi-square (χ^2) test and Student's t test have evaluated associations between the categorical and continuous variables. The logistic regression model was used to find the risk variables for patients by including all variables in the model and to calculate the odds ratios. The receiver operator characteristic (ROC) curve analysis was used to establish the discriminative factors for appendiceal metastasis. All variables were included in the backward stepwise procedure. p values were considered statistically significant at $p<0.05$. Statistical analyses were carried out by using the statistical packages for SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

There were 134 patients with epithelial ovarian cancer in our study. All of them had undergone a surgical staging procedure including appendectomy. Of these, 21 (15.7%) had appendiceal metastasis. Two of these metastasis were microscopic in which the histologic sections were positive for disease and the appendix was noted to be grossly normal by the operating surgeon and pathologist. But these two microscopic involvement did not lead upstaging of tumor as both of them had intraabdominal metastatic spread. Demographic parameters including patient's age, parity and family history of ovarian or breast cancer were statistically similar between the cases and controls ($p>0.05$) (Table 1). The difference between the groups with regard to mean preoperative Ca125 levels was not statistically significant ($p=0.926$). However, maximal primary ovarian tumor diameter was significantly higher in cases than in controls ($p=0.001$). No appendiceal metastasis was detected patients with apparent stage I disease. This rate was 9.5% in apparently stage II disease, 66.7% in stage III, and 23.8% in stage IV disease. The controls were distributed by stage as follows: 22.1% stage I, 54.9% stage II, 19.5% stage III, and 3.5% stage IV. The distribution of patients by stage of disease was significant between the groups ($p=0.000$). Appendiceal metastasis was found in 0.0%, 23.8%, and 76.2% of cases with grade I, II, and III tumors, respectively. This distribution was significantly different according to the grade distribution of controls ($p=0.001$). The rate of ascites presence was 90.5% in cases which was significantly greater than in controls ($p=0.000$). Patients with appendiceal metastasis had 81.0% presence of malignant peritoneal cytology, whereas the patients with no appendiceal metastasis had 43.4% positive peritoneal cytology ($p=0.002$).

Table 1. Demographic and Clinicopathologic Features of Patients

		Cases (N=21)	Controls (N=113)	p*
Age		55.62±4.06	55.27±4.13	0.718
Parity		3.19±1.81	3.50±1.72	0.460
Family History		4 (19.0)	13 (11.5)	0.340
Preoperative Ca125 (U/ml)		254.29±182.48	250.16±187.83	0.926
Diameter of ovarian tumor		9.19±2.38	7.35±2.15	0.001
Stage	I	0 (0.0)	25 (22.1)	0.000
	II	2 (9.5)	62 (54.9)	
	III	14 (66.7)	22 (19.5)	
	IV	5 (23.8)	4 (3.5)	
Grade	I	0 (0.0)	8 (7.1)	0.001
	II	5 (23.8)	69 (61.1)	
	III	16 (76.2)	36 (31.9)	
	Ascites presence	19 (90.5)	25 (22.1)	0.000
	Positive peritoneal cytology	17 (81.0)	49 (43.4)	0.002
Hystopathologic Subtype	Serous	13 (61.9)	80 (70.8)	0.533
	Mucinous	4 (19.0)	21 (18.6)	
	thers	4 (19.0)	12 (10.6)	
Site of tumor	Unilateral right-sided &bilateral	10 (47.6)	7 (6.2)	0.000
	Left sided	11 (53.4)	106 (93.8)	

*$p<0.05$ was considered statistically significant; Values were given as mean±standard deviation or number (percentage)

Table 2. Multivariate Analysis of Risk Factors for Appendiceal Metastasis

	Wald	p*	OR	CI
Ascites presence	5,255	0.022	0.092	0.012-0.708
Positive peritoneal cytology	1,741	0.187	4,234	0.496-36.118
Unilateral right sided&bilateral	8,047	0.005	16,698	2.387-116.801
Age ≥55 years	0.013	0.909	1,106	0.197-6.196
Stage>2	5,757	0.016	16,376	1.669-160.709
Hystopathologic subtype	3,551	0.060	5,332	0.935-30.402
Grade >2	5,228	0.022	7,815	10.341-45.541
Ca125 ≥500 U/ml	1,523	0.217	4,424	0.41-46.9527
Diameter ≥10 cm	5,834	0.016	11,491	10.585-83.335

* p<0.05 was considered statistically significant

Table 3. Table 3: Areas Under ROC Curve for Stage, Grade and Maximal Diameter of Tumor

	AUC	SE	p*	95 % CI
Stage	0.818	0.051	0.000	0.717-0.918
Grade	0.730	0.057	0.001	0.619-0.841
Diameter	0.705	0.055	0.003	0.597-0.813

* p<0.05 was considered statistically significant; AUC: Area Under Curve; SE:Standar Error; CI: Confidence Interval

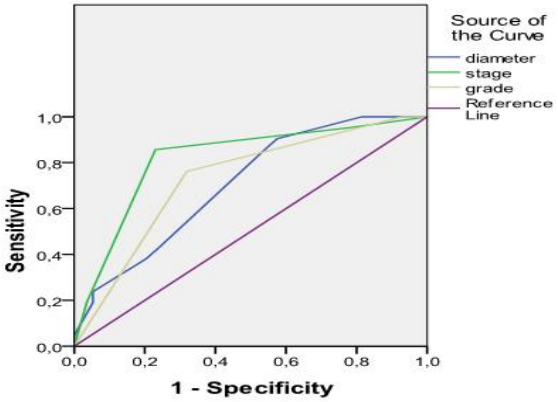

Figure 1. Receiver Operating Characteristics of Stage, Grade and Maximal Diameter of Tumor for Appendiceal Metastasis. Diagonal segments are produced by ties

With respect to histopathologic diagnosis, there was no significant difference between the cases and controls (p=0.533). Appendiceal metastasis rate in unilateral right-sided tumor was higher than in bilateral or unilateral left-sided tumors. Bilateral and right sided rate of ovarian cancer in cases (47.6%) was significantly higher than the rate in controls (6.2%) (p=0.000) (Table 1).

In multivariate analysis, the variables cathegorized as risk factors for appendiceal metastasis were evaluated (Table 2). Stage >2 (p=0.016, odds ratio (OR)=16.37, 95% confidence interval (CI)=1.669-160.709), grade >2 (p=0.022, OR=7.815, 95%CI=10.341-45.541), presence of ascite (p=0.022, OR=0.092, 95%CI=0.012-0.708), maximal ovarian tumor diameter ≥10cm (p=0.016, OR=11.491, 95%CI=10.585-83.335) and bilateral-right sided localization of ovarian tumor (p=0.005, OR=16.698, 95%CI=2.387-116.801) were the factors to be significant for the appendiceal metastasis (Table 2).

A ROC curve was drawn to demonstrate the selectivity of stage, grade and maximal diameter of tumor for appendiceal metastasis (Figure 1). The area under curve was 0.818±0.051 (p=0.000; 95%CI 0.597-0.813) for stage; 0.730±0.057 (p=0.001; 95%CI 0.619-0.841) for grade; 0.705±0.055 (p=0.003; 95%CI 0.597-0.813) for maximal diameter of tumor (Table 3).

Discussion

Ovarian cancer spreads typically throughout the abdominopelvic cavity. Thus it is important to determine the extent of the disease spread accurately and to remove as much of the tumor as possible at the time of surgical staging and cytoreductive surgery. Although appendix is suggested as a frequent metastatic site for epithelial ovarian carcinoma, pathological data of appendix especially in early stage ovarian cancer do not absolutely support this. So that routine removal of the appendix during surgery for ovarian cancer remains a topic of controversy (Ramirez et al., 2006). However in mucinous ovarian cancer, appendectomy is advised to perform routinely (Kleppe et al., 2014). In our study, 15.7% (21/134) of patients had appendiceal involvement. 9.5% (2/21) of metastasis to the appendix were observed in stage I and II tumors. 90.5% (19/21) metastasis to the appendix were noted in stages III and IV ovarian carcinomas which was the highest rate of literature. And stage of the tumor was the most discriminative factor (AUC=0.818) (Figure 1) for appendiceal metastasis in epithelial ovarian cancer. Sonnendocker (1982), who was the first to demonstrate the high frequency of appendiceal involvement in epithelial ovarian cancers, reported an 83.3% metastatic rate in his small study of 12 stage III-IV patients. In subsequent reports by Malfetano (1987), Rose et al. (1991) and Takac (2000), similar high rates were also reported in stage III-IV disease (69.7%, 69-75%, and 54.2%, respectively). However in patients with early-stage ovarian cancer, the appendix is rarely involved as evidenced by previous studies showing the rate of appendiceal metastasis in patients with early ovarian cancer to be ranged from 0-9% (4,9,10). Furthermore, 90.5% (19/21) metastasis to the appendix was grossly observed during staging surgery, while two patients (9.5%) had only a microscopically identifiable tumor. Appendectomy did not change the stage of the disease in any of the patients. Because all had gross metastatic intraabdominal involvement. Likewise, Malfetano (1987), Fontanelli et al. (1992) and Bese et al. (1996) reported similar rate of microscopic appendiceal involvement in their studies and none of the patients was upstaged in their studies because of having intraabdominal metastatic spread. However, in the largest series published to date, Ayhan et al. (2005) found that patients who underwent appendectomy at the time of primary cytoreductive surgery for epithelial ovarian cancer, had a rate of 37% appendiceal metastasis. They also noted that 5% of patients with apparent stage I-II disease had their disease upstaged because of isolated appendiceal metastases. The investigators concluded that routine appendectomy is indicated in all patients with epithelial ovarian carcinoma as part of the initial surgical staging because of the considerable possibility of upstaging in patients with early disease and the chance for optimal cytoreduction in patients with advanced disease.

We found that histological grade >2 was a significant

risk factor for appendiceal metastasis (AUC=0.730, p=0.001) (Figure 1). Our study deviates from the results of Bese and colleagues (1996) who observed no relationship between histological grade and metastasis to the appendix in their series. However, Rose et al. (1991) concluded that, in comparison with grade I and II ovarian tumors, grade III tumors metastasize to the appendix more frequently.

Another risk factor that we investigate was the histopathologic subtype of tumor. In our study we found 61.9% of appendiceal metastasis to be of serous and 19.0% of mucinous subtype. Mucinous ovarian tumor have been the least studied of ovarian tumors and prior appendectomy has been reported not to protect against developement of subsequent malignant mucinous ovarian tumor (Elias et al., 2013) There was no significant difference between appendiceal metastasis and histopathologic subtypes as Ayhan et al. (2005) found in his study. However, Rose et al. (1991) and Fontanelli et al. (1992) had showed sinificantly more appendiceal involvement in patient with serous histopathology.

In this study, there was no significant relationship between appendiceal metastasis and preoperative Ca 125 levels. On the contrary, Ayhan et al. (2005) found that Ca125 level higher than 500 U/ml was found to be significantly related to appendiceal metastasis.

In multivariate analysis, presence of peritoneal cytology was not found to be significant for appendiceal metastasis, even though it was more frequent with appendiceal involvement. On the other hand, maximal diameter of tumor ≥10cm was found to be significant factor determining the appendiceal metastasis in multivariate analysis. These findings did deviate from the results of Ayhan and collegues (2005) who reported that positive peritoneal cytology was a sigificant risk factor while maximal diameter of tumor ≥10 cm was not.

We found that presence of ascites was a significant determinant of appendiceal metastasis. This finding support those of previous studies in literature (Fontanelli et al.,1992; Bese et al., 1996; Ayhan et al., 2005). The drainage pathway of the ascites through the paracolic space which is close to appendix may promote appendiceal maetastasis.

Fontanelli et al. (1992), reported a higher prevalence of appendiceal involvement in patients with right-sided tumors. Similarly, appendiceal metastasis rate in right-sided tumor was higher than in bilateral or left-sided tumors in our study. It is possible that the location of appendix proximity to the right ovary contributes to its invasion more frequently by tumor.

In conclusion, our data confirm that in epithelial ovarian cancer stage, grade, right-sided location, large tumor size and presence of ascite have an important value as a predictor of appendiceal metastasis. When we compare our findings with previous studies, there isn't any definite agreement for the risk factors of appendiceal metastasis. Further studies with more participants are needed for an absolute definition of risk factors pointing out the appendiceal metastasis in epithelial ovarian cancer.

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