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Primary and metastatic mucinous adenocarcinomas of the ovary: Evaluation of the diagnostic approach using tumor size and laterality

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Abstract

Objective. To evaluate the usefulness of the recently proposed algorithm (Seidman JD, Kurman RJ, Ronnett BM. Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis. Am J Surg Pathol 2003;27:985–93 [5]) that classifies mucinous adenocarcinomas of the ovary as primary when they were unilateral ≥10 cm and as metastatic when they were unilateral <10 cm or bilateral.

Methods. Malignant ovarian neoplasms, which were resected in Chiang Mai University Hospital between 1992 and 2003, were histologically reviewed. Mucinous adenocarcinomas involving the ovary were identified. The medical records and radiologic materials were reviewed in correlation with the pathologic features to identify the primary site.

Results. There were 74 cases of mucinous adenocarcinomas; 16 were primary ovarian; 52, metastatic; and 6 of indeterminate primary site (primary versus metastatic). Primary mucinous adenocarcinomas had a mean size of 16.4 cm and bilateral involvement in 13%. Metastatic mucinous adenocarcinomas had a mean size of 11.7 cm and bilateral involvement in 77%. Excluding the 6 tumors of indeterminate primary site, the proposed algorithm correctly classified primary and metastatic tumors in 84% of 68 cases. Of 21 unilateral mucinous adenocarcinomas ≥10 cm, 62% were primary ovarian. Of 5 unilateral tumors <10 cm, 80% were metastatic. Of 42 bilateral mucinous adenocarcinomas, 95% were metastatic.

Conclusion. The algorithm provided high accuracy in the overall prediction of primary and metastatic mucinous adenocarcinomas of the ovary, with major strength in the identification of metastatic tumors by bilaterality or size <10 cm. However, the prediction of primary mucinous adenocarcinomas by unilaterality and size ≥10 cm was less reliable than previously reported. Due to the overlapping features between primary and metastatic tumors and the higher frequency of the latter, the possibility of metastases should always be borne in mind in the evaluation of mucinous adenocarcinomas of the ovary.

Keywords: Ovary; Mucinous tumor; Mucinous adenocarcinoma; Primary tumor; Metastatic tumor; Tumor size; Tumor laterality

Introduction

The ovary is a frequent site for metastatic involvement [1]. Metastatic mucin-producing adenocarcinomas to the ovary frequently cause diagnostic confusion with primary ovarian mucinous adenocarcinoma [2–5]. As ovarian metastatic lesions can be the initial presentation of the patients without previously recognized primary cancers, the metastatic nature of the tumor is not suspected preoperatively in many cases [6–8]. Careful intraoperative exploration of the intra-abdominal organs and intraoperative pathology consultation is important in the evaluation and diagnosis of metastatic tumors. However, intraoperative distinction between primary and metastatic mucinous adenocarcinomas on frozen sections can be difficult. In a recent study of primary and metastatic mucinous adenocarcinomas in the ovaries, Seidman et al. proposed an algorithm based on tumor size and laterality that correctly classified mucinous adenocarcinomas in 90% of all 50 cases and 83% of tumors after the exclusion of signet ring cell carcinomas and primary microinvasive tumors [5]. Based on the proposed algorithm, mucinous adenocarcinomas were classified as

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primary when the tumors were unilateral and ≥10 cm (correct prediction 82%) and as metastatic when they were bilateral or unilateral and <10 cm (correct prediction 95%). This algorithm is simple and may serve as a useful guide in the intraoperative evaluation of ovarian mucinous adenocarcinomas [5].

In another series comparing metastatic mucinous adenocarcinomas and selected stage I primary mucinous adenocarcinomas of the ovary, Lee and Young [4] reported a greater proportion of metastatic mucinous adenocarcinomas >10 cm compared to that of Seidman et al. (48% versus ~34%) [5]. The bilaterality rate of metastatic tumors in both studies was comparable (75%). Combination of tumor size and laterality was not evaluated in Lee and Young's study [4]. It is uncertain whether the proposed algorithm would provide a similar result in different settings. We believe that the algorithm should be tested for its reproducibility in another hospital series before applying to routine practice. The purpose of this study was to review primary and metastatic mucinous adenocarcinomas in our practice setting and evaluate the usefulness of the algorithm using tumor size and laterality in the diagnosis.

Materials and methods

Consecutive cases of malignant ovarian neoplasms, either primary or metastatic, were searched from the surgical pathology files of the Department of Pathology, Faculty of Medicine, Chiang Mai University (CMU) between January 1992 and December 2003 (12-year period). The histologic slides were reviewed, and the diagnoses were classified according to the 2003 WHO classification [9]. Distinction between primary and metastatic tumors was based on recent diagnostic criteria [2–4,10]. Clinicopathologic data of all metastatic tumors (hospital and referral cases) were reported in another study [11]. For inclusion in this study, the ovaries had been resected at CMU Hospital. The diagnosis of primary mucinous adenocarcinoma required exclusion of the possibility of metastatic tumors by reviewing the medical records, radiologic materials, and available follow-up outcome. Advanced-stage mucinous adenocarcinomas showing suggestive features, but not fulfilling the diagnostic criteria for metastases [2,10] and not having definite extraovarian primary tumors, were considered as tumors of indeterminate primary site (primary versus metastatic). Metastatic tumors with microscopic ovarian involvement were excluded because they rarely cause diagnostic problems.

Metastatic invasive adenocarcinomas with at least some degree of mucin production were classified as mucin-producing adenocarcinomas. Determination of primary sites for metastatic tumors was based on the clinicopathologic review. For the diagnosis of metastatic tumors of unknown primary site, the pathologic features of the ovarian lesions must be diagnostic of metastases [2,10]. Metastatic mucin-producing adenocarcinomas were further classified, based on the predominant component (involving >50% of the histologic materials), into the following groups: mucinous adenocarcinoma, adenocarcinoma with predominant endometrioid-like (pseudoendometrioid) appearance, and signet ring cell carcinoma. Only the metastatic mucinous adenocarcinoma group was further analyzed and compared with primary and indeterminate mucinous adenocarcinomas.

The data regarding age, tumor size (maximal dimension), and laterality of all cases of mucinous adenocarcinomas (primary, metastatic and indeterminate) were collected. The histologic features of all mucinous adenocarcinomas were recorded including architectural grade and the presence of the following features: confluent epithelial pattern, nodular growth pattern, surface implants, ovarian hilar involvement, lympho-vascular space invasion, minor signet ring cell component, and co-existing ovarian lesion [2,4]. Architectural grading was based on the proportion of solid tumor area as follows: grade 1, <5%; grade 2, 5–50; and grade 3, >50%. Confluent epithelial pattern was defined by complex arrangement of malignant epithelial cells, with little or no intervening stroma, exceeding 10 mm^2 in area [2,9,10]. Co-existing primary ovarian lesions must be clearly different from mucinous adenocarcinoma components. A benign or borderline (low malignant potential) mucinous tumor component was not considered as a co-existing ovarian lesion for primary mucinous adenocarcinoma. For evaluation of the proposed algorithm [5], cases of primary and metastatic mucinous adenocarcinomas were tabulated by laterality (unilateral versus bilateral) and tumor size (<10 versus ≥10 cm).

Results

During the study period, there were 238 cases of primary ovarian epithelial carcinomas resected at CMU Hospital, 16 of which (6.7%) were primary mucinous adenocarcinomas. Primary mucinous adenocarcinomas were stage I in 11 cases (69%), stage II in 2 (13%), stage III in 2 (13%), and stage IV in 1 case (6%). There were 6 mucinous adenocarcinomas of indeterminate primary site (primary versus metastatic). Ninety cases of metastatic mucin-producing adenocarcinomas to the ovary were identified. The large intestine was the most common primary site for ovarian metastases (29 cases or 32%). For further analysis of metastatic mucinous adenocarcinomas, 15 adenocarcinomas with predominant endometrioid-like appearance and 23 signet ring cell carcinomas were excluded. The excluded tumors originated from the large intestine (17 cases), stomach (10 cases), appendix (2 cases), cervix (1 cases), and unknown primary site (8 cases).

Table 1 shows information on 74 mucinous adenocarcinomas including 16 primary ovarian; 52 metastatic; and 6 of

Table 1
Comparison of selected clinicopathologic features of mucinous adenocarcinomas involving the ovary in each category (primary, metastatic, and indeterminate primary site)

Category	No.	Mean age (range) (year)	Mean size (range) (cm)	Bilaterality (%)	Size <10 cm (%)	Unilateral and size ≥10 cm (%)
Primary	16	48 (32–75)	16.4 (8.0–25.0)	2 (13)	1 (6)	13 (81)
Metastatic	52	49 (21–85)	11.7 (3.0–29.0)	40 (77)	22 (42)	8 (15)
Large intestine	12	46 (27–66)	13.8 (5.0–29.0)	9 (75)	4 (33)	2 (17)
Intrahepatic bile duct	10	54 (41–74)	11.4 (3.0–20.0)	6 (60)	4 (40)	3 (30)
Extrahepatic bile duct and gallbladder	7	52 (21–66)	11.1 (6.0–17.0)	7 (100)	4 (57)	0
Stomach	2	59 (32–85)	11.8 (11.0–12.5)	2 (100)	0	0
Appendix	2	58 (54–61)	19.5 (19.0–20.0)	2 (100)	0	0
Breast	2	31 (26–35)	4.5 (4.0–5.0)	2 (100)	2 (100)	0
Cervix	10	47 (31–63)	10.6 (5.0–18.0)	6 (60)	5 (50)	2 (20)
Unknown	7	48 (32–62)	10.8 (5.0–21.0)	6 (86)	3 (43)	1 (14)
Indeterminate primary site	6	60 (49–75)	12.8 (6.5–20.0)	4 (67)	2 (33)	1 (17)

Fig. 1. Metastatic mucinous adenocarcinoma from the colon. The 13.0-cm solid-cystic tumor showed multicystic appearance with abundant thick mucous content.

indeterminate primary site. Primary mucinous adenocarcinomas had a mean size of 16.4 cm (range 8.0–25.0) and bilateral involvement in 13%. Metastatic mucinous adenocarcinomas had a mean size of 11.7 cm (range 3.0–29.0) and bilateral involvement in 77%. In 10 of 52 (19%) metastatic mucinous adenocarcinomas, tumors with bilateral involvement presented grossly with unilateral dominant enlargement of the ovarian masses. The biliary tract (intra- and extrahepatic bile duct/gallbladder), colon, and cervix were the major primary sites for metastatic mucinous adenocarcinomas. Metastatic tumors from all sites except the breast had a mean size >10 cm (Figs. 1 and 2).

Table 2
Comparative histologic features of primary, metastatic, and indeterminate mucinous adenocarcinomas

	Primary (%)	Metastatic (%)	Indeterminate (%)
Architectural grade 1	12 (75)	36 (69)	5 (83)
Confluent epithelial pattern	11 (69)	8 (15)	2 (33)
Nodular growth pattern	1 (6)	24 (46)	2 (33)
Surface implants	1 (6)	20 (38)	5 (83)
Hilar involvement	0	15 (29)	2 (33)
Vascular invasion	0	8 (15)	1 (17)
Focal signet ring cells	0	9 (17)	1 (17)
Co-existing ovarian lesion	1 (6)	3 (6)	0
Total	16 (100)	52 (100)	6 (100)

Table 2 shows comparison of histologic features between each category of ovarian mucinous adenocarcinomas. The confluent epithelial pattern was much more common in primary tumors than in metastases. The nodular pattern, surface implants, and hilar involvement were uncommon in primary mucinous adenocarcinomas. Foci of signet ring cells were observed in 9 cases of metastatic tumors from the large intestine (4), breast (2), appendix (1), cervix (1), and unknown primary (1), but in none of primary mucinous adenocarcino-

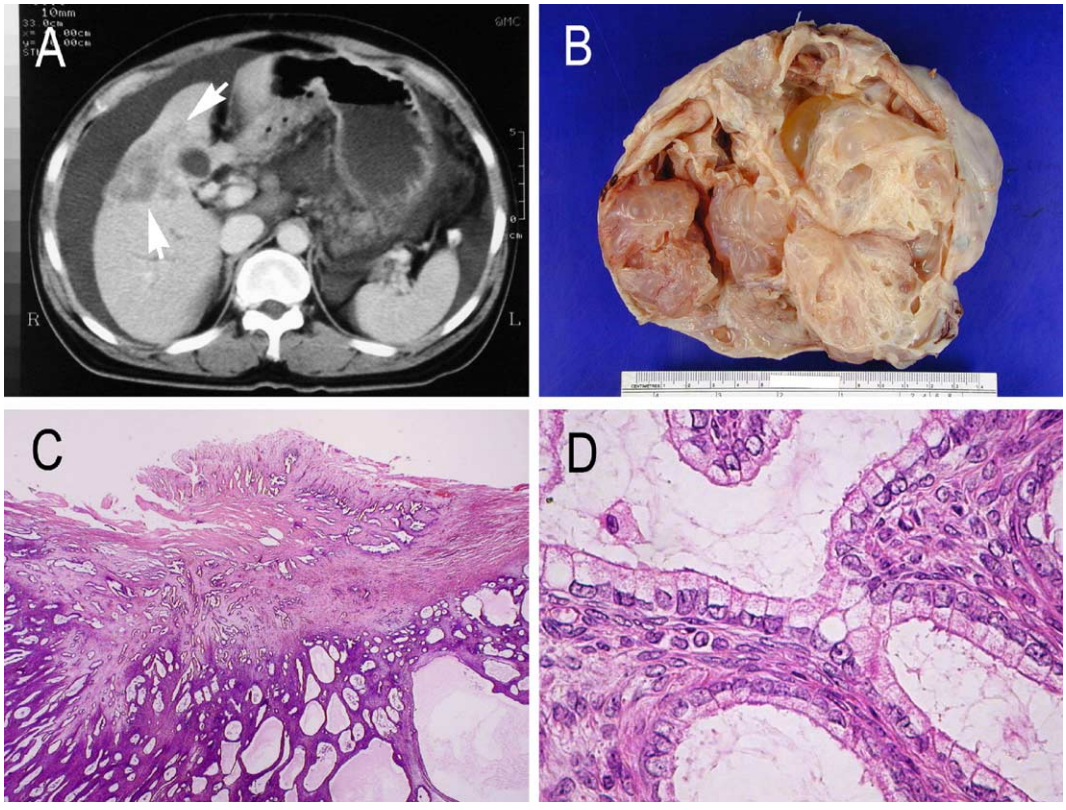

Fig. 2. Metastatic mucinous adenocarcinoma from intrahepatic cholangiocarcinoma. Post-contrast enhanced CT scan showed a 5-cm irregular inhomogeneous enhancing hypodense mass (arrows) in hepatic segments 4–5 and ascites (A). The 16.0-cm right ovarian mass was multicystic (B). Histologic section showed a desmoplastic surface implant of adenocarcinoma overlying disorderly infiltrative glands and variable-sized cysts (C). Many glands and cysts were lined by a single layer of atypical mucinous epithelium, simulating a PRIMARY ovarian tumor (D). The left ovarian mass was 17.0 cm and had similar gross and microscopic appearances (not shown).

Table 3
Distribution of primary and metastatic mucinous adenocarcinomas divided by laterality and size <10 and ≥10 cm

	Size <10 cm (%)	% in each category	Size ≥10 cm (%)	% in each category
Unilateral				
Primary (n = 14)	1 (20)	7	13 (62)	93
Metastatic (n = 12)	4 (80)	33	8 (38)	67
	5 (100)		21 (100)	
Bilateral				
Primary (n = 2)	0	0	2 (8)	100
Metastatic (n = 40)	18 (100)	45	22 (92)	55
	18 (100)		24 (100)	

mas. Co-existing ovarian lesions were observed in 1 of 16 (6%) primary tumors and 3 of 52 (6%) metastatic tumors (2 from the large intestine and 1 from the intrahepatic bile duct). The co-existing lesion in primary mucinous adenocarcinoma was mature cystic teratoma. The primary ovarian lesions in metastatic cases included 1 mature cystic teratoma, 1 mucinous cystadenoma, and 1 Brenner tumor.

Table 3 shows the distribution of primary and metastatic mucinous adenocarcinomas categorized by tumor size (<10 versus ≥10 cm) and laterality (unilateral versus bilateral). Of these 68 cases, the algorithm correctly identified the primary or metastatic nature in 57 cases (84%). Of 21 unilateral mucinous adenocarcinomas ≥10 cm, 62% were primary ovarian. Of 5 unilateral tumors <10 cm, 80% were metastatic. The large majority of primary mucinous adenocarcinomas (94% or 15 of 16 cases) were ≥10 cm compared to 58% (30 of 52 cases) of metastatic tumors. Of 42 bilateral mucinous adenocarcinomas, 95% were metastatic.

Discussion

Distinction between primary and metastatic mucinous adenocarcinomas of the ovary has long been a diagnostic challenge to pathologists [12]. Recently, there has been significant progress in diagnostic criteria to distinguish between primary and metastatic tumors [2,4,10]. Recent studies on mucinous adenocarcinomas of the ovary suggested that primary tumors should be much less common than previously reported, and published data on primary ovarian mucinous adenocarcinomas in the literature might be unreliable, probably due to the inclusion of metastatic tumors and mucinous borderline (low-malignant potential) tumors [5,12,13]. The proportion of mucinous adenocarcinoma within primary ovarian epithelial carcinomas was only 2.4% in a recent study [5], and it was 6.7% in ours, compared to the average proportion of 12% in previous reports (range 6–25%) [5]. Metastatic mucinous adenocarcinomas were reported to be much more common than primary tumors, with a ratio of metastatic to primary tumors up to 3.2:1 [5]. A similar proportion of metastatic to primary mucinous adenocarcinomas was also observed in our study.

There was some difference in the distribution of primary sites of metastatic mucinous adenocarcinomas in our study compared to that in the Western series [2,4,5]. The pancreas was one of the most common primary sites for metastatic mucinous adenocarcinomas to the ovary in the Western reports, whereas it was uncommon in our study. In contrast, the biliary tract (intra- and extrahepatic bile duct/gallbladder) was a major source of ovarian metastatic tumors in our practice, but this was unusual in Western studies. The findings may, at least in part, be explained by the difference in cancer incidence rates between Western populations and Thai people [14]. The mean age for primary and metastatic mucinous adenocarcinomas in our study was comparable to that in the Western reports [4,5], except for metastatic tumors of the large intestine, which occurred in a younger age group than those of Western women (mean age 46 years versus 55–60 years) [6,15,16]. Metastatic mucinous adenocarcinomas in our study tended to be larger than those reported by Seidman et al. (tumor size ≥10 cm in 58% versus 34%) [5].

Bilaterality was observed in approximately 75% of metastatic tumors but was uncommon in primary mucinous adenocarcinomas at an early stage [4,5,12]. The tumor size of metastatic tumors in several reports was also <10 cm [2,5,8,17,18]. The algorithm using tumor size and bilaterality to distinguish between primary and metastatic tumors was developed on the basis of these observations and provided high diagnostic accuracy in the original study (83–90%) [5] and our setting (84%). In each subgroup divided by bilaterality and tumor size, the accuracy of metastasis prediction by bilaterality was 95%, and by size <10 cm in unilateral tumors 80%, which was comparable to Seidman et al.'s results [5]. However, in the subgroup of unilateral tumors ≥10 cm, the proportion of primary mucinous adenocarcinomas was only 62% compared to the previously reported proportion of 82% [5]. The main reason for this discrepancy was the larger size of metastatic tumors in our study compared to those of Seidman et al. [5]. The large size of metastatic tumors was not limited only to the mucinous adenocarcinoma group because the mean size for each non-ovarian primary cancer remained almost unchanged when signet ring cell carcinomas and adenocarcinomas with endometrioid-like appearance were included (mean 14.0 cm for colorectal origin and 11.1 cm for gastric origin). This may, in part, be associated with delayed medical consultation in our population, which resulted in the detection of ovarian metastases when they had reached a large size.

The histologic features of mucinous adenocarcinomas listed in Table 2 were chosen from the findings in the recent series of selected hospital and consultation cases by Lee and Young [4]. The usefulness of these features was confirmed in our study, which represented the setting in daily practice. A confluent epithelial pattern was present in most primary mucinous adenocarcinomas, whereas the presence of a nodular pattern, surface implants, and hilar involvement was consistent with metastases. The majority of tumors of indeterminate primary site were probably metastatic tumors of unknown primary site. The presence of co-existing ovarian lesions such as mature teratoma, Brenner tumor, or endometriosis has been considered as strong supporting evidence for the diagnosis of primary mucinous adenocarcinoma [4]. However, such findings should

be interpreted with care and should not prevent a diagnosis or suspicion of metastatic tumor.

It is important that gynecologists and pathologists maintain a high index of suspicion for metastatic tumors in the diagnostic approach of ovarian tumors [12]. Having a high level of suspicion for metastatic disease for mucinous adenocarcinoma involving the ovary is warranted due to the much greater frequency of metastatic tumors and relative rarity of primary ovarian mucinous adenocarcinomas. In the intraoperative consultation of ovarian tumors, the diagnostic criteria should be sensitive for the detection of metastases. The impression that unilateral mucinous adenocarcinoma ≥10 cm should be primary ovarian, based on the algorithm, may lead to an underestimation of the possibility of metastasis. The surgeons' clinical biases for primary ovarian tumors may result in failure to convey the information to pathologists regarding other possible primary tumors (i.e. remote or recent history of other cancers, the presence of non-ovarian tumors, or unusual distribution of tumor involvement) that would be important clues in the diagnostic approach for metastatic tumors to the ovary [3,10]. In addition, presentation of bilateral metastatic tumors with unilateral dominant ovarian masses can easily lead to the clinical impression of primary tumors. If the contralateral ovary is not diligently examined by either surgeon or pathologist, bilateral involvement may not be documented.

The usefulness of the proposed algorithm was to classify mucinous adenocarcinomas as metastatic tumors by bilaterality or size <10 cm [5]. However, the reverse (unilateral tumor ≥10 cm) was not highly predictive of primary mucinous adenocarcinoma. Lee and Young commented in their study that tumor size alone was unreliable in the distinction between primary and metastatic mucinous adenocarcinomas [4]. They also suggested that a size >15 cm was common for primary mucinous adenocarcinomas, but uncommon in metastases. However, the proportion of tumors classified by such a criterion was not reported. Further divisions of all mucinous adenocarcinomas in our study by a size of 15 cm resulted in the data shown in Table 4. Of 13 unilateral tumors ≥15 cm, 69% were primary ovarian. Primary mucinous adenocarcinomas of the ovary were ≥15 cm in 69% (11 of 16 cases) compared to 35% (18 of 52 cases) of metastatic mucinous adenocarcinomas. Unilateral tumors ≥15 cm were observed in 56% (9 of 16 cases) of primary mucinous adenocarcinomas compared to only 8% (4 of 52 cases) of metastatic tumors.

Despite the unreliability of a large tumor size to distinguish primary from metastatic mucinous adenocarcinoma, it was more likely that unilateral tumors ≥15 cm were primary ovarian and tumors smaller than 10 cm were metastatic. Based on the results in Table 4, unilateral tumors with size between 10 and 15 cm should be considered as indeterminate, and the intraoperative diagnosis would be based better on other clinical findings and pathologic features such as surface implants, nodular growth pattern, hilar involvement, and signet ring cell component [3,4,10], although these pathologic details may be difficult to detect in the limited samples for intraoperative frozen sections. In these cases, another primary tumor should be carefully searched for intraoperatively, and subsequently, careful specimen sampling for histologic examination is essential for the diagnosis. Postoperative or follow-up repeat investigations may also be required in some cases [3]. Immunohistochemical stains, particularly for cytokeratins 7 and 20, may help in the differential diagnosis. However, the usefulness of such stains was limited to metastases from large intestine as metastatic tumors from most other sites had overlapping immunohistochemical profiles (cytokeratin 7 + cytokeratin 20 + or −) with ovarian mucinous adenocarcinomas [12,19–23]. Due to the overlapping features between primary and metastatic mucinous adenocarcinomas, the possibility of metastatic tumors should be borne in mind regardless of large tumor size and unilaterality. The final diagnosis of primary ovarian mucinous adenocarcinoma should be based on a complete clinicopathologic evaluation.

Table 4
Distribution of primary and metastatic mucinous adenocarcinomas divided by laterality and size <10, 10 to <15, and ≥15 cm

	Size <10 cm (%)	Size 10 to <15 cm (%)	Size ≥15 cm (%)
Unilateral			
Primary (n = 14)	1 (20)	4 (50)	9 (69)
Metastatic (n = 12)	4 (80)	4 (50)	4 (31)
	5 (100)	8 (100)	13 (100)
Bilateral			
Primary (n = 2)	0 (0)	0 (0)	2 (13)
Metastatic (n = 40)	18 (100)	8 (100)	14 (87)
	18 (100)	8 (100)	16 (100)

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