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Chromosomal gains in the sarcomatoid transformation of chromophobe renal cell carcinoma

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The hallmark of chromophobe renal cell carcinoma is multiple chromosomal losses from among chromosomes 1, 2, 6, 10 and 17. Chromophobe renal cell carcinoma with distant metastases or sarcomatoid transformation are uncommon and little is known about their chromosomal abnormalities. We collected six sarcomatoid chromophobe renal cell carcinomas and three primary chromophobe renal cell carcinomas with distant metastases. A cytogenetic analysis by fluorescent *in situ* hybridization on paraffin-embedded tissue was performed using centromeric probes for chromosomes 1, 2, 6, 10 and 17. We found more than one signal in four of six (66%) sarcomatoid chromophobe renal cell carcinomas, in both sarcomatoid and adjacent epithelial components. Both primary chromophobe renal cell carcinomas and matched metastases showed single signals for all chromosomes studied in two cases and no abnormalities in the remaining case. We concluded that: (1) both epithelial and sarcomatoid components of sarcomatoid chromophobe renal cell carcinoma show different genetic abnormalities from those characteristic of chromophobe renal cell carcinoma; (2) sarcomatoid chromophobe renal cell carcinomas frequently have multiple gains (polysomy) of chromosomes 1, 2, 6, 10 and 17; (3) distant metastases show the same genetic patterns, usually chromosomal losses (monosomy), found in the primary tumors.
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Most chromophobe renal cell carcinomas are low stage, cured by surgery and have a relatively good prognosis.[1] Losses of chromosomes 1, 2, 6, 10 and 17 are frequent genetic abnormalities in both classic and eosinophilic chromophobe renal cell carcinomas.[2] Chromophobe renal cell carcinomas with distant metastases or sarcomatoid transformation are uncommon.[3–6] Most have been reported as single cases[7–23] and few cytogenetic data are available.[24] We sought to identify cytogenetic characteristics of sarcomatoid and metastatic chromophobe renal cell carcinomas by interphase fluorescence *in situ* hybridization (FISH) analysis.

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Materials and methods

Tissue Samples, Histochemical and Immunohistochemical Analyses

We collected six chromophobe renal cell carcinomas with sarcomatoid transformation and three primary chromophobe renal cell carcinomas with matched distant metastases. Two cases with sarcomatoid features were collected from the Department of Pathology, Indiana University Medical Center and four from University Hospital Plzen, Czech Republic. The three metastatic tumors were respectively collected by Hôpital Européen Georges Pompidou, Paris, France, Istituto Europeo di Oncologia, Milan, Italy and Department of Pathology of Innsbruck University, Austria. Seven cases have been reported previously.[20,23]

For all formalin-fixed and paraffin-embedded tumors, serial 5 μm sections were stained with

hematoxylin and eosin, with Hale's colloidal iron technique and immunostained with antibodies recognizing the following markers: parvalbumin (PA-235, Sigma Chemical Company, St Louis, MO, USA; dilution, 1:500), cytokeratin 7 (protease, 1:50; DAKO, Carpinteria, CA, USA) and vimentin (steam, 1:100; Zymed, San Francisco, CA, USA). Immunoreactions were developed using a non-biotin, highly sensitive system (Envision peroxidase detection system, DAKO, Carpinteria, CA, USA) preventing possible false-positive staining due to endogenous biotin present in the tissues.

FISH Analysis

FISH analysis was performed on five normal tissue samples: two of normal renal parenchyma adjacent to the epithelial component of sarcomatoid chromophobe renal cell carcinomas and three of normal tissue adjacent to metastatizing chromophobe renal cell carcinomas. FISH analysis was performed on all tumors.

From each tumor, 5 μm sections were cut from paraffin-embedded blocks. The paraffin was removed from the sections with two 10-min washes in xylene. After hydrating in 100, 85, and 70% ethanol solutions (10 min), rinsing in distilled water (10 min), and twice in phosphatebuffer solution (pH 7, 10 min each), the slides were fixed in methanol–acetic acid 3:1 for 10 min and air-dried. Next, the sections were treated in a 2 $\times$ standard saline citrate solution for 15 min at 37°C, and then dehydrated in consecutive 70, 85, and 100% ethanol solutions for 1 min each and then dried. Next, the sections were bathed in 0.1 mM citric acid (pH 6) solution at 85°C for 1 h. Then they were again dehydrated in a series of ethanol solutions and dried. The tissue was digested by applying 0.75 ml of pepsin (Sigma, St Louis, MO, USA) solution (4 mg/ml in 0.9% NaCl, pH 1.5) to each slide and incubating them in a humidified box for 30 min at 37°C. Next, the slides were rinsed with distilled water for few seconds, dehydrated again in graded ethanol solutions and dried. Centromeric probes for chromosomes 1, 2, 6, 10 and 17 (Vysis, Downers Grove, IL, USA) were used. Each probe was diluted 1:100 in tDenHyb1 buffer (Insitus, Albuquerque, NM, USA). Ten microliters of diluted probe were applied to each slide and cover slips were placed over the slides. Denaturation was achieved by incubating the slides at 80°C for 10 min in a humidified box; then hybridization was performed at 37°C for 3 h. The cover slips were then removed and the slides were immersed at room temperature in 0.5 $\times$ SSC for 2 min, in 50% formamide/1 $\times$ SSC for 5 min, and in 2 $\times$ SSC for 2 min. The slides were air dried and counterstained with 10 μl DAPI/Antifade (DAPI in Fluorguard, 0.5 μg/ml, Insitus, Albuquerque, NM, USA).

The slides were examined using an Axioplan (Zeiss, Germany) with appropriate filters for SpectrumOrange (centromeric probes 1 and 2, Abbott), SpectrumGreen (centromeric probes 6, 10 and 17, Abbott), and the UV Filter for the DAPI nuclear counterstain. The signals were recorded with a CCD camera (Axiocam HRm).

Fluorescent *in situ* signals were evaluated according with previous reports.[2,25–27] From 100 to 200 neoplastic nuclei were counted and scores followed distinction between sarcomatoid and epithelial components.

Results

Pathological Findings

Admixed with the epithelial component of six chromophobe renal cell carcinomas were extensive areas of sarcomatoid spindle cells (Figure 1) with frank nuclear pleomorphism and high mitotic activity (Figure 2).

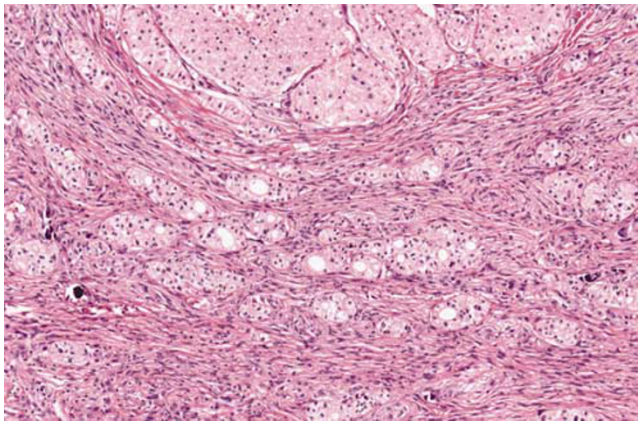

Figure 1 Sarcomatoid chromophobe renal cell carcinoma (hematoxylin and eosin stain, $\times$ 20).

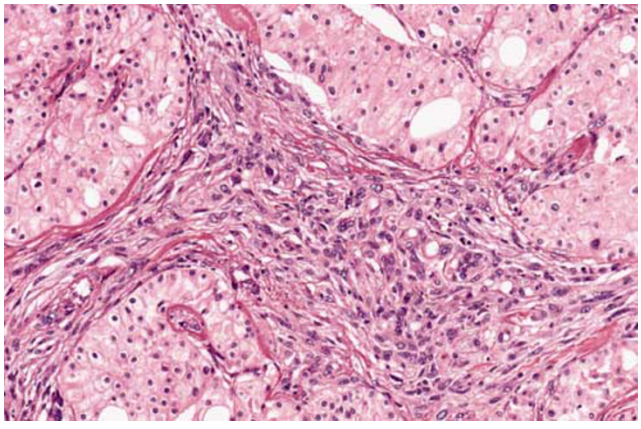

Figure 2 Sarcomatoid chromopobe renal cell carcinoma: epithelial areas intermixed with sarcomatous ones (hematoxylin and eosin stain, $\times$ 40).

The pulmonary, pancreatic and retro-peritoneal lymph-nodal metastases of three chromophobe renal cell carcinomas, respectively, occurred 10, 12 and 5 years after surgery.

Hales' colloidal iron stain showed diffuse cytoplasmic positivity in both primary and metastatic lesions of all three metastatic chromophobe renal cell carcinomas and in the epithelial component of all sarcomatoid chromophobe renal cell carcinomas whereas their sarcomatous components displayed patchy staining. Parvalbumin was diffusely positive in all epithelial component of the sarcomatoid chromophobe renal cell carcinomas and both primary and metastatic chromophobe renal cell carcinomas. CK7 was focally positive in the epithelial component of three sarcomatoid chromophobe renal cell carcinomas (5–15% of neoplastic cells) and in one primary and metastatic chromophobe renal cell carcinoma. Vimentin was positive in the sarcomatoid component of five out of six but it was negative in the epithelial chromophobic cells. Sarcomatous components did not label both parvalbumin and CK7 antibodies.

FISH Analysis

Normal tissue samples
Two fluorescent signals were found from 64 to 82% of nuclei. Three fluorescent signals were found in no more than 16% of nuclei (Table 1). These findings overlap those described previously in normal renal parenchyma adjacent to chromophobe renal cell carcinomas without sarcomatoid component[2,25–27] and for this reason we used equal cutoffs to summarize numerical genetic abnormalities observed in the tumors.

Sarcomatoid chromophobe renal cell carcinomas
The results are present in Table 2 and summarized in Table 3.

DAPI fluorescent stain allowed the distinction between the epithelial neoplastic islands and the sarcomatous areas (Figure 3). We found more than one signal for most chromosomes in four of six (66%) sarcomatoid chromophobe renal cell carcinomas (cases no. 1, 2, 4, 5) (Figure 4) in both sarcomatoid and adjacent epithelial components. In the epithelial components of two sarcomatoid chromophobe renal cell carcinomas single signals were, respectively, found for chromosomes 1, 2, 6 and 1, 6, 10 (cases no. 3 and 6).

Metastatic chromophobe renal cell carcinomas
The results are present in Table 2 and summarized in Table 3.

Both primary chromophobe renal cell carcinomas and matched pulmonary and pancreatic metastases showed single signals for all chromosomes studied. Differently, two signals were found in both primary and matched lymph-nodal metastases for all chromosomes studied.

Discussion

In this study, we demonstrate that (1) sarcomatoid chromophobe renal cell carcinomas have different genetic abnormalities from those characteristic of this histotype, sharing more than one signal of chromosomes 1, 2, 6, 10 and 17 in both epithelial and sarcomatoid components, (2) distant metastases of chromophobe renal cell carcinoma display the same genetic pattern as the primary tumors and (3) interphase cytogenetic findings by FISH analysis of aggressive chromophobe renal cell carcinoma suggest that chromosomal gains are important for the sarcomatoid transformation of chromophobe renal cell carcinoma but not for its metastatic potential.

The genetic hallmark of chromophobe renal cell carcinomas is the loss of multiple chromosomes from among the chromosomes 1, 2, 6, 10 and 17 (2). Our FISH analysis demonstrates that numerical chromosomal changes in sarcomatoid chromophobe renal cell carcinoma are different from those found in chromophobe renal cell carcinoma composed only of carcinoma. We found more than one signal for most of the tested chromosomes in four of

Table 1 Percentages of different signal number in nuclei from normal tissue

No. case	*Chromosome 1*			*Chromosome 2*			*Chromosome 6*			*Chromosome 10*			*Chromosome 17*		
	Percentage of nuclei			*Percentage of nuclei*			*Percentage of nuclei*			*Percentage of nuclei*			*Percentage of nuclei*		
	1 sign.	*2 sign.*	*≥3 sign.*	*1 sign.*	*2 sign.*	*≥3 sign.*	*1 sign.*	*2 sign.*	*≥3 sign.*	*1 sign.*	*2 sign.*	*≥3 sign.*	*1 sign.*	*2 sign.*	*≥3 sign.*
Normal renal parenchima adjacent to chromophobe RCC with sarcomatoid transformation															
1	18	72	10	20	76	4	23	71	6	21	76	3	20	74	6
2	19	76	5	22	74	4	12	82	6	13	78	9	15	73	12
Normal parenchima adjacent to chromophobe RCC with distant metastases															
1	22	72	6	24	64	12	13	70	16	15	75	10	21	69	20
2	12	80	8	11	78	11	11	80	9	25	71	4	19	68	13
3	23	75	2	20	66	14	28	65	7	17	72	11	10	80	10

Table 2 Percentages of nuclei with different numbers of signals from neoplastic cells

No. case	*Chromosome 1*			*Chromosome 2*			*Chromosome 6*			*Chromosome 10*			*Chromosome 17*		
	Percentage of nuclei			*Percentage of nuclei*			*Percentage of nuclei*			*Percentage of nuclei*			*Percentage of nuclei*		
	1 sign.	*2 sign.*	*≥3 sign.*	*1 sign.*	*2 sign.*	*≥3 sign.*	*1 sign.*	*2 sign.*	*≥3 sign.*	*1 sign.*	*2 sign.*	*≥3 sign.*	*1 sign.*	*2 sign.*	*≥3 sign.*
Chromophobe RCC with sarcomatoid transformation															
1 Epithelial	18	75	7	14	83	3	15	79	6	11	79	10	14	69	17
1 Sarcomatoid	12	38	50	19	21	60	31	51	18	17	40	43	23	42	35
2 Epithelial	16	75	9	24	64	12	14	66	20	22	70	8	22	68	10
2 Sarcomatoid	20	41	39	15	44	41	12	30	58	12	35	53	5	39	56
3 Epithelial	76	20	4	78	17	5	82	14	4	15	82	3	23	60	17
3 Sarcomatoid	56	34	10	63	27	10	78	16	6	12	40	48	24	40	36
4 Epithelial	12	20	68	17	30	53	12	22	66	20	36	44	21	47	32
4 Sarcomatoid	10	25	65	9	26	65	11	20	69	12	33	55	20	22	58
5 Epithelial	10	44	46	12	33	55	9	55	36	7	33	60	10	44	46
5 Sarcomatoid	12	55	33	8	33	59	12	34	54	18	45	37	5	23	72
6 Epithelial	86	10	4	12	80	8	43	55	2	86	10	4	11	88	1
6 Sarcomatoid	18	45	37	15	45	40	18	45	37	13	44	43	6	44	50
Chromophobe RCC with distant metastases															
7 Primary	84	12	4	86	10	4	80	10	10	80	17	3	76	21	3
7 Pulmonary mts	82	12	6	82	10	8	78	19	3	79	12	9	86	12	2
8 Primary	89	8	3	80	13	7	80	15	5	82	13	5	65	30	5
8 Pancreatic mts	71	20	9	72	22	6	68	18	14	75	15	10	73	17	10
9 Primary	12	78	10	12	80	8	15	80	5	11	82	7	19	78	3
9 Lymph-nodal mts	13	81	6	16	75	9	21	73	6	12	80	8	15	83	2

Table 3 Pattern chromosomal summary in aggressive chromophobe renal cell carcinomas

No. case	*Chromosome number*				
	Chromosome 1	*Chromosome 2*	*Chromosome 6*	*Chromosome 10*	*Chromosome 17*
Chromophobe RCC with sarcomatoid transformation					
1 Epithelial	Dysomy	Dysomy	Dysomy	Dysomy	Dysomy
1 Sarcomatoid	Polysomy	Polysomy	Monosomy	Polysomy	Polysomy
2 Epithelial	Dysomy	Dysomy	Dysomy	Dysomy	Dysomy
2 Sarcomatoid	Polysomy	Polysomy	Polysomy	Polysomy	Polysomy
3 Epithelial	Monosomy	Monosomy	Monosomy	Dysomy	Dysomy
3 Sarcomatoid	Monosomy	Monosomy	Monosomy	Polysomy	Polysomy
4 Epithelial	Polysomy	Polysomy	Polysomy	Polysomy	Polysomy
4 Sarcomatoid	Polysomy	Polysomy	Polysomy	Polysomy	Polysomy
5 Epithelial	Polysomy	Polysomy	Polysomy	Polysomy	Polysomy
5 Sarcomatoid	Polysomy	Polysomy	Polysomy	Polysomy	Polysomy
6 Epithelial	Monosomy	Dysomy	Monosomy	Monosomy	Dysomy
6 Sarcomatoid	Polysomy	Polysomy	Polysomy	Polysomy	Polysomy
Chromophobe RCC with distant metastases					
7 Primary	Monosomy	Monosomy	Monosomy	Monosomy	Monosomy
7 Pulmonary mts	Monosomy	Monosomy	Monosomy	Monosomy	Monosomy
8 Primary	Monosomy	Monosomy	Monosomy	Monosomy	Monosomy
8 Pancreatic mts	Monosomy	Monosomy	Monosomy	Monosomy	Monosomy
9 Primary	Dysomy	Dysomy	Dysomy	Dysomy	Dysomy
9 Lymph-nodal mts	Dysomy	Dysomy	Dysomy	Dysomy	Dysomy

six (66%) sarcomatoid chromophobe renal cell carcinomas in both the sarcomatoid and adjacent epithelial component. Differently, two out of three metastatic chromophobe renal cell carcinoma showed one signal for all chromosomes in both primary and metastatic chromophobe renal cell carcinomas. We conclude that these multiple chromosomal gains could play a role for sarcomatoid transformation of chromophobe renal cell carcinoma and do not characterize metastatic chromophobe renal cell carcinoma, neither in the renal primary nor in the metastases.

In the largest series reported to date, Akhtar *et al*[24] presented six cases of sarcomatoid chromophobe

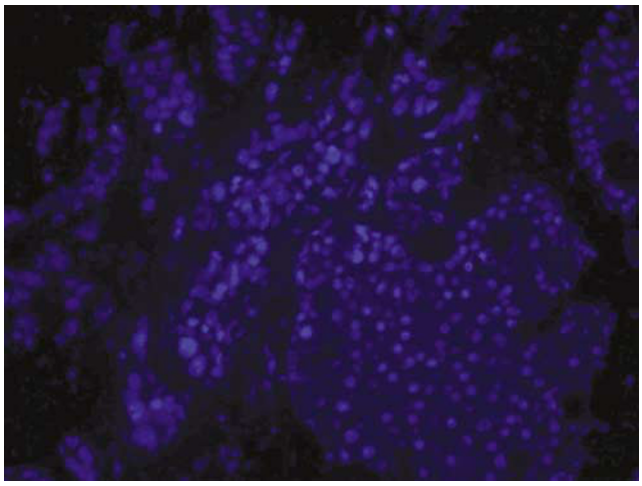

Figure 3 Sarcomatoid chromophobe renal cell carcinoma: DAPI fluorescent counterstain on formalin-fixed paraffin embedded tissue allows distinction between epithelial and sarcomatous components (× 40).

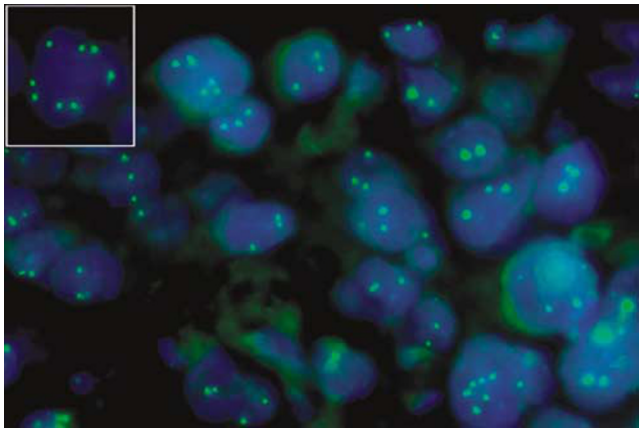

Figure 4 Sarcomatoid chromophobe renal cell carcinoma: FISH analysis showing numerical chromosome 17 gains (SpectrumGreen, × 63).

renal cell carcinoma. DNA ploidy analysis revealed that progression to high-grade sarcomatoid areas was associated with the development of pronounced aneuploidy, while the areas of the typical chromophobe renal cell carcinoma were near-diploid or even hypodiploid. Our data are in agreement with those findings. Again, our case no. 3 is even similar to the two cases described by Akhtar *et al*[10] and Cserni *et al*[14] in distinctive reports sharing a predominantly hypodiploid pattern in both sarcomatoid and epithelial component.

Sarcomatoid renal cell carcinomas are generally considered to be the result of a process of dedifferentiation of an epithelial type of renal cell carcinoma and one would expect that the dedifferentiated malignant cells would conserve the original genomic changes that characterize the malignant epithelial tumor cells from which they are thought to be derived.[28] However, different cytogenetic data have been reported. Most analyses have shown complex chromosomal rearrangements, suggesting the alteration of multiple genes in sarcomatoid transformation of clear cell and papillary renal cell carcinomas. Dal Cin *et al*[29] combined their results with a few other cases from the literature, and concluded that genomic changes in most sarcomatoid renal cell carcinomas appeared to have little in common with those characterizing the underlying carcinoma. However in three studies, 10 of 13 sarcomatoid tumors demonstrated the specific genetic change associated with the clear cell subtype, that is loss of (part of) 3p.[29–31] Cheng *et al* studied sarcomatoid clear cell renal cell carcinoma and found that X-chromosome inactivation analysis provide strong evidence for a common progenitor cell origin for both the clear cell and sarcomatoid components. However, in the same study the authors found by loss of heterozygosity analysis a genetic heterogeneity within both components and they concluded that although molecular heterogeneity was clearly present, the data did not provide sufficient evidence to establish a multistep model for neoplastic transformation and progression in renal cell carcinomas.[32] Two sarcomatoid papillary renal cell carcinomas were described to have complex karyotypes with no abnormalities in common between epithelial and sarcomatoid areas of the same tumor[33] but a case report showed trisomy of chromosome 7 and 17 in sarcomatoid papillary renal cell carcinoma in both components.[34] In 12 sarcomatoid renal cell carcinomas without any distinction among the renal cell histotypes of the carcinomatous component, Jiang *et al*[35] found either losses than gains with an average of 8.6 aberrations per tumor and concluded that sarcomatoid renal cell carcinomas are genetically complex.

In this study, we examined selected chromosomes that usually characterize chromophobe renal cell carcinomas without sarcomatoid component, thus we do not exclude the fact that other molecular abnormalities, in association with those found, can play a role or be the prime factor in the sarcomatoid transformation of chromophobe renal cell carcinomas.

Application of molecular techniques to the study of renal epithelial neoplasms have been widely used.[36] The interphase FISH analysis used in our study has the advantage of allowing evaluation of fluorescent signals with distinction between sarcomatoid and epithelial components of the same tumor.

Our results demonstrate that metastatic chromophobe renal cell carcinomas show the same genetic pattern in both primary and metastatic tumors. A very few data reporting the genetic analysis in both primary and metastatic chromophobe renal cell carcinoma are present in the literature. Renshaw *et al* reported a DNA ploidy analysis of a primary chromophobe renal cell carcinoma which metastatized to the liver, revealing a diploid pattern.[37] This

pattern is similar to one of our case (no. 9) which metastatized to the lymph-nodes. Dijkhuizen *et al*[38] reported chromosomal changes in a splenic metastasis of a chromophobe renal cell carcinoma showing in addition to the extensive chromosome losses specific for the chromophobe subtype, structural rearrangements involving chromosomes 1, 5, 12, 15 and 18. They concluded that determining whether or not the observed structural changes were important for the metastatic behavior of chromophobe renal cell carcinomas still remained unclear. Among other histotypes various gains and losses of DNA sequence copy number have been found when comparing primary clear cell or papillary renal cell carcinomas and metastatic lesions.[39–44]

The histochemical and immunohistochemical analyses showed results as expected, regarding the epithelial component.[23,45,46] Parvalbumin and CK7 showed immunoexpression in the chromophobic cells whereas vimentin was absent; Hale's colloidal iron stain was diffusely positive. Moreover sarcomatoid component of chromophobe renal cell carcinomas displayed a patchy staining with Hale's colloidal iron and did not for parvalbumin and CK7.

In conclusion, our interphase cytogenetic findings by FISH analysis of aggressive chromophobe renal cell carcinomas suggest that multiple chromosomal gains are important for the sarcomatoid transformation of chromophobe renal cell carcinoma but not for its metastatic potential.

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