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Prognostic factors for relapse in stage I seminoma: a new nomogram derived from three consecutive, risk-adapted studies from the Spanish Germ Cell Cancer Group (SGCCG)

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Background: We aimed to analyze prognostic factors for relapse in stage I seminoma managed by either active surveillance or adjuvant chemotherapy, and to describe the long-term patterns of recurrence in both groups.

Patients and methods: From 1994 to 2008, 744 patients were included in three consecutive, prospective risk-adapted studies by the Spanish Germ Cell Cancer Group. Low-risk patients were managed by surveillance and high-risk patients were given two courses of adjuvant carboplatin. Relapses were treated mainly with chemotherapy. Patient age, tumor size, histological variant, pT staging, rete testis invasion, and preoperative serum BHCG levels were assessed for prediction of disease-free survival (DFS).

Results: After a median follow-up of 80 months, 63 patients (11.1%) have relapsed: 51/396 (14.8%) on surveillance and 12/348 (3.2%) following adjuvant carboplatin. Actuarial overall 5-year DFS was 92.3% (88.3% for surveillance versus 96.8% for chemotherapy, $P = 0.0001$). Median time to relapse was 14 months. Most recurrences were located at retroperitoneum (86%), with a median tumor size of 26 mm. All patients were rendered disease-free with chemotherapy (92%), radiotherapy (5%), or surgery followed by chemotherapy (3%). A nomogram was developed from surveillance patients that includes two independent, predictive factors for relapse: rete testis invasion and tumor size (as a continuous variable).

Conclusion: Long-term follow-up confirms the risk-adapted approach as an effective option for patients with stage I seminoma. The pattern of relapses after adjuvant chemotherapy is similar to that observed following surveillance. A new nomogram for prediction of DFS among patients on surveillance is proposed. Rete testis invasion and tumor size should be taken into account when considering the administration of adjuvant carboplatin. Prospective validation is warranted.

Key words: seminoma, stage I, surveillance, adjuvant carboplatin, prognostic factors

introduction

Testicular cancer is the most common malignancy in young males and constitutes the paradigm of a curable neoplasm [1]. The majority of patients are diagnosed between the ages of 16 and 34. About 50% are seminomas, and 80%–85% present with stage I disease, thus representing the most frequent clinical setting. Three treatment approaches are now available for stage I seminoma patients (i.e. active surveillance, adjuvant carboplatin, and prophylactic radiation therapy) that offer similar, excellent outcomes [2]. Almost all patients become long-term survivors,

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so that late effects of any treatment are of upmost importance [3]. The availability of reliable prognostic factors for relapse would help to treatment individualization in order to minimize toxicity.

In 2002, Warde et al. published a pooled analysis of 638 patients with stage I seminoma managed by surveillance, and found that invasion of the rete testis and tumor size >4 cm were independent predictors of cancer relapse [4]. The Spanish Germ Cell Cancer Group (SGCCG) started in 1994 a series of risk-adapted studies in this setting [5]. The second [6] and third [7] studies incorporated these prognostic factors in order to tailor the selective use of adjuvant carboplatin, thus indirectly validating their negative predictive value [8]. In contrast, other two recent publications could not confirm their clinical value in large series [9, 10]. In these studies, notably, information about the status of rete testis involvement was absent in many cases (33% and 100%, respectively).

The purpose of the present study was to analyze prognostic factors for relapse in stage I seminoma managed by either surveillance or adjuvant carboplatin. Mature, updated results of these three risk-adapted studies with a long-term follow-up were used to ensure a large population of patients treated with one of these two options. The pattern of recurrences and their clinical outcome was also evaluated in order to reinforce the efficacy of this individualized management approach.

patients and methods

Between 1994 and 2008, 744 consecutive patients with stage I seminoma were included in three prospective, SGCCG risk-adapted studies. Patient characteristics, treatment strategies, and clinical outcome have been previously published with median follow-up times of 52, 34, and 34 months, respectively [5–7]. In brief, after orchiectomy patients were staged by means of clinical history, physical examination, chest X-ray films, computed tomography (CT) of abdomen and pelvis, ultrasonography of the contralateral testicle, whole blood cell counts, and serum chemistries including lactate dehydrogenase, α-fetoprotein (AFP), and β-human chorionic gonadotropin (BHCG). Informed consent for this risk-adapted policy was attained before group allocation, and a central, prospective, and anonymized registration at the SGCCG data center was used. In the first study (initiated before the publication of the pooled analysis of Warde et al.), patients with vascular invasion and/or >T1 tumors received adjuvant carboplatin (400 mg/m^2 for two cycles, 28 days apart) whereas those presenting without such risk factors were managed by surveillance. In the second study, the risk factors used for carboplatin administration were tumor size >4 cm and/or invasion of rete testis. In the third one, we restricted adjuvant chemotherapy to patients with both risk criteria. These latter two studies employed carboplatin at the standard dose nowadays (AUC 7 for two courses, every 21 days). Follow-up schedules for patients under surveillance and after adjuvant chemotherapy have been homogeneous throughout studies. In both groups, clinical history, physical examination, chest X-rays, AFP, and BHCG were scheduled at months 3, 6, 9, 12, 18, 24, 30, 36, 48, 60, and 72 months after orchiectomy, and abdominal CT scans were carried out at 6, 12, 18, 24, 30, 36, 48, 60, and 72 months. After this time, patients were visited at the discretion of the attending physician. The recommended approach for tumor recurrences was chemotherapy with either four courses of etoposide and cisplatin (EP) [11] or three courses of conventional bleomycin, etoposide, and cisplatin (BEP) [1], independently of the initial management and the time elapsed from orchiectomy. Here, we report updated results with a more prolonged follow-up time. Individual patient data were collected from hospital records with the last cutoff date in December 2012.

Potential predictive factors for relapse were prospectively recorded, including patient age (≤30 versus >30 years), tumor size (≤4 versus >4 cm), histological variant (classical versus anaplastic), pT stage (pT1–2 versus pT3–4), presence of vascular invasion, rete testis invasion, and preoperative BHCG levels (negative versus positive). Histological features were reviewed locally. Numerical parameters were also assessed as continuous variables. To compare proportions between groups, Pearson's χ^2 or Fisher's exact tests (when appropriate) were used. Cause-specific disease-free survival (DFS) was estimated from the date of orchiectomy to the date of relapse or death from any cause (only relapses were considered events) with the Kaplan–Meier method. Relapse rates and incidence of contralateral germ-cell tumors were also reported as Kaplan–Meier estimates. Comparison of resulting curves and univariate analysis of prognostic factors were carried out with the log-rank test. For multivariate analysis of DFS, we used the Cox proportional hazard method. According to its results, a nomogram was developed for predicting individual risks of relapse among patients on surveillance. Akaike information criterion (AIC) was used to select the best predictive model. As a measure of discrimination we computed a 10-fold cross-validated Somers' Dxy rank correlation. We also assessed calibration of the model by plotting bias-corrected estimates of predicted versus observed values by bootstrapping.

results

Median follow-up time from orchiectomy was 80 months (range, 24–204 months). Sixty-three patients (11.1%) have so far relapsed: 51/396 (14.8%) on active surveillance and 12/348 (3.2%) after adjuvant carboplatin ($P = 0.0001$). Actuarial overall DFS was 92.3% at 5 years and 90.7% at 10 years. At the time of this report, 147 patients (19.8%) have been observed for 2–5 years (due to loses to follow-up or inclusion in the most recent study), 420 (56.4%) for 5–10 years, and 177 (23.8%) for >10 years. Long-term follow-up shows that a small number of additional (late) relapses have occurred in all three series after the initial publications (supplementary Table S1, available at *Annals of Oncology* online). Median time to relapse in patients with tumor recurrence was 13.7 months (range, 3–138 months). Seventy-six percent of all relapses occurred in the first 2 years and 90.5% in the first 3.5 years. Six relapses (9.5% of recurrences, or 0.8% of all patients) occurred after 5 years (at 61, 62, 68, 98, 107, and 138 months). Recurrences were located at retroperitoneum (85.7%), pelvic nodes (6.3%), spermatic cord (1.6%), mesenterium (1.6%), and lung (1.6%), while raised BHCG levels was the only sign of relapse in two cases (3.2%). Median tumor size at recurrence was 26.5 mm (range, 0–90 mm). Methods of detection were routine CT scans (74.6%), raised BHCG levels (20.6%), and symptoms of disease (4.8%). Salvage therapy was effective so that all patients were rendered disease-free with chemotherapy (92%), radiation therapy (5%), or surgery plus chemotherapy (3%). EP was employed in 48 patients whereas BEP was used in 10 cases. There were no significant differences in any of these clinical features between relapses occurred on surveillance and those detected after adjuvant carboplatin (supplementary Table S2, available at *Annals of Oncology* online). The incidence of second malignancies, either testicular (5 versus 6 cases) or extragonadal (6 versus 6 patients), was also similar in both treatment groups (supplementary Table S3, available at *Annals of Oncology* online).

Table 1 depicts the univariate analysis of prognostic factors for relapse. As aforementioned, the incidence of recurrences was significantly lower in high-risk patients treated with adjuvant carboplatin than that observed in low-risk patients managed by surveillance. Among patients on surveillance, invasion of rete testis, tumor size >4 cm, and pT >2 attained statistical significance whereas histological subtype was of borderline significance. Multivariate analysis showed that invasion of rete testis and tumor size (continuous variable) were independent predictors of DFS. Considering patients treated with carboplatin, only invasion of rete testis was predictive of relapse in uni- and multivariate analyses. An interval between orchiectomy and start of adjuvant chemotherapy >60 days was associated with a higher risk of recurrence. In contrast, the method of carboplatin dose calculation (mg/m^2 versus AUC) was not related with the incidence of relapses (data not shown). In the whole series of patients with stage I seminoma, invasion of rete testis, adjuvant chemotherapy, patient age, and serum BHCG levels (the latter as continuous variables) were independent prognostic factors for relapse.

Table 1. Univariate analysis of predictive factors: 5-/10-year disease-free survival rates among clinical and pathological categories

Number of patients	Surveillance (396)	Carboplatin (348)	All patients (744)
Feature	88.3%/85.2%	96.8%/96.8%	92.3%/90.7%
Age (years)			
≤30	148	116	264
	87.1%/86.0%	94.8%/94.8%	90.5%/89.9%
>30	247	231	478
	89.0%/84.7%	97.8%/97.8%	93.3%/91.1%
P	NS	0.065	NS
Tumor diameter (cm)			
≤4	274	55	329
	91.2%/89.3%	96.4%/96.4%	92.1%/90.6%
>4	110	285	395
	82.6%/76.9%	96.8%/96.8%	92.8%/91.0%
P	0.016	NS	NS
Preoperative serum BHCG positive*			
Yes	41	64	105
	82.9%/82.9%	95.3%/95.3%	90.5%/90.5%
No	334	257	591
	88.9%/85.2%	97.3%/97.3%	92.5%/90.5%
P	NS	NS	NS
Histological subtype			
Classical	385	329	714
	88.8%/85.5%	96.6%/96.6%	92.4%/90.7%
Anaplastic	9	18	27
	66.7%/66.7%	100%/100%	88.9%/88.9%
P	0.053	NS	NS
Staging (pT)			
pT1–2	357	175	532
	90.5%/88.0%	98.3%/98.3%	93.0%/91.3%
pT3–4	37	171	208
	67.6%/61.4%	95.3%/95.3%	90.3%/89.0%
P	<0.0001	0.099	NS
Vascular invasion**			
Yes	30	144	174
	86.7%/86.7%	95.8%/95.8%	94.2%/94.2%
No	358	197	555
	88.5%/85.1%	97.5%/97.5%	91.7%/89.5%
P	NS	NS	NS
Rete testis invasion***			
Yes	52	180	232
	74.9%/64.5%	95.0%/95.0%	90.4%/87.7%
No	342	166	508
	90.6%/88.6%	98.8%/98.8%	93.3%/92.1%
P	<0.0001	0.021	NS

Data available in *696 (93.5%), **729 (98%), and ***740 (99.5%) patients.
NS, nonsignificant; BHCG, β-human chorionic gonadotropin.

Thus, in a second step, a new predictive model was formulated. To avoid bias, only surveillance patients were included in the model. Vascular and rete testis invasion were included as dichotomous variables, while tumor size, age, and serum BHCG levels were considered as continuous variables. A Cox proportional hazard method-based model was developed to predict the occurrence of relapses at three years. The best model (AIC) included two clinical/pathological variables significantly associated with an increased risk of recurrence: presence of rete testis invasion ($P < 0.001$) and tumor size ($P = 0.052$). A nomogram was proposed that is available to predict an individual patient probability of DFS (Figure 1) . Both calibration and discrimination of the model were good, with no evident bias in the calibration plot and a Somers' Dxy = 0.28.

DFS curves for all three studies are shown in Figure 2A. Actuarial DFS was significantly better for study II than for studies I and III at the expense of a greater percentage of patients treated with carboplatin (68% versus 30% and 33%, respectively). When combining studies II and III, the cumulative relapse rate among patients with no risk factors (tumor size <40 mm and no rete testis invasion) was 8.3%. Figure 2B shows the outcome of patients managed with either surveillance or adjuvant chemotherapy. No patient has died as a result of seminoma so that 5-year cause-specific survival is 100%.

discussion

There are now several acceptable management strategies for stage I testicular seminoma after orchiectomy: adjuvant radiotherapy, introduced in the 1950s; active surveillance with treatment reserved for those who relapse, introduced in the 1980s; and adjuvant chemotherapy with carboplatin, introduced in the 1990s. Cure rates are high for all strategies, with 5-year survival in experienced centers of 98%–100% [1–3]. However, the optimum management strategy remains controversial, and current patterns of care are highly variable among countries and specialists [10, 12–15]. Radiotherapy use is clearly decreasing worldwide because it is associated with a low but significant risk of second malignancies; while surveillance is preferred in countries like Canada and Denmark, chemotherapy is more frequently used in Norway, Sweden, and Australia. The choice is a matter of patient and clinician preference, based on balancing toxicity and patient circumstance. Contemporary international guidelines increasingly recommend surveillance as the preferred management strategy for willing and able patients [8, 16–18].

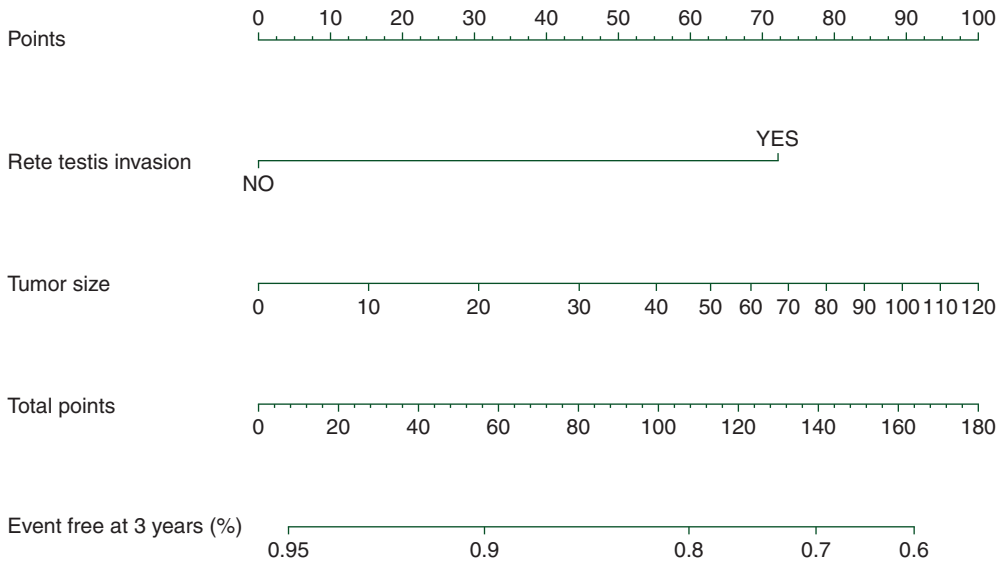

Figure 1. Nomogram for prediction of 3-year disease-free survival (derived from surveillance patients). The first line is a reference line for reading scoring points for each variable. Once the sum of total points is calculated, the predicted value can be read at the bottom.

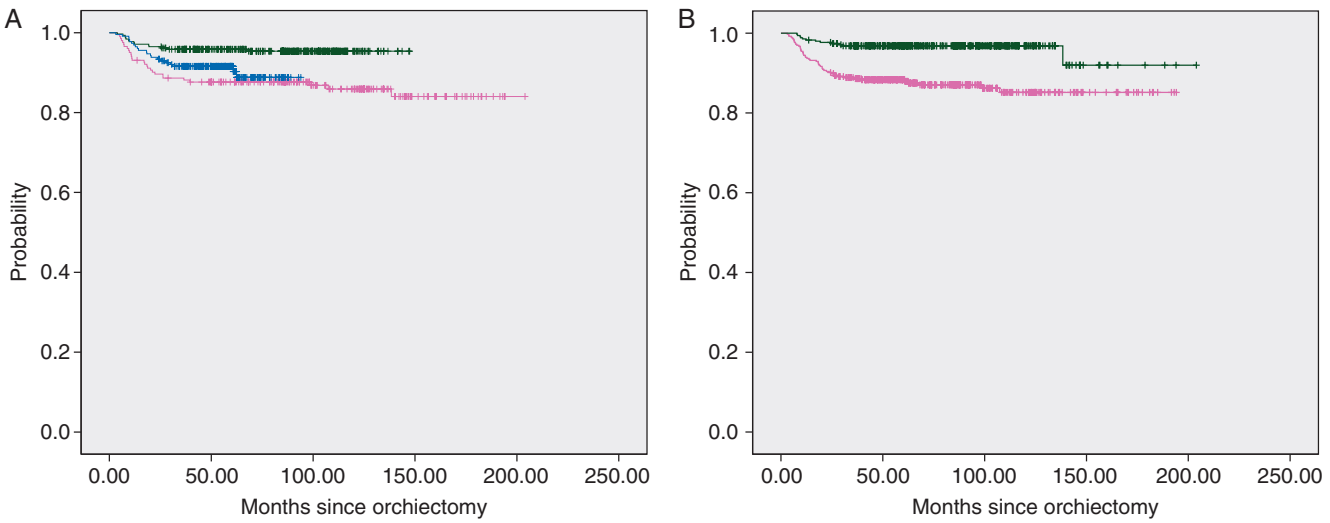

Figure 2. Actuarial disease-free survival (DFS) curves. (A) Comparison of studies I (pink curve), II (green curve), and III (blue curve). Respective DFS for studies were: study I (87.7% at 5 years and 85.9% at 10 years), study II (95.9% at 5 years and 95.4% at 10 years), and study III (91.6% at 5 years and 88.8% at 10 years). $P = 0.002$ for II versus I and III. (B) Comparison of surveillance (pink curve) versus adjuvant carboplatin (green curve). DFS was 88.3% at 5 years and 85.2% at 10 years for patients on surveillance, versus 96.8% at 5 and 10 years for those treated with chemotherapy, $P < 0.0001$.

A fourth treatment option is the risk-adapted approach. It is an entirely rational strategy because it avoids treatment-related morbidity for patients whose disease was cured by orchiectomy and restricts adjuvant therapy for those at a higher risk of relapse. As far as we know, only the SGCCG has prospectively tested this option [5–7]. Now, with mature data from 744 patients followed for more than 6 .5 years (range, 2–18 years), we can state that this approach is effective. Our 11.1% relapse rate compares favorably with the 15%–20% attained in the surveillance studies [3, 4, 10], and the proportion of men treated with adjuvant therapy in our trials (46.8% overall) is significantly lower than in the studies of carboplatin or radiation therapy (100%). We have also demonstrated that the incidence of relapses among patients with no risk factors (tumor size <4 cm and no rete testis invasion) is only 8.3%. Mortality due to seminoma was zero in this multicenter setting. Furthermore, no significant differences in the pattern of recurrences or outcome were observed between patients on surveillance and those treated with adjuvant carboplatin. Late relapses do occur in both groups and, although curable, should be taken into account for designing follow-up strategies. Finally, with only 3.2% relapse rate in the subgroup of adjuvant carboplatin, comprehensive radiological surveillance may be avoided.

The incidence of second testicular neoplasms in our patients managed by surveillance was similar than in those who received adjuvant carboplatin (although latency time was shorter). This

is in contrast with the significant reduction in the medium term of risk of second germ-cell tumors reported after chemotherapy in a randomized trial against radiotherapy [19]. Possible explanations are differences in follow-up schedules, patient numbers, and follow-up duration. Other primary cancers occurred with the same frequency in both groups and, although not formally addressed, no other late complications have been observed. This is in concordance with other studies with larger number of patients [19] or longer follow-up [20] in which no excess of overall mortality, deaths from circulatory disease or the incidence of second cancers (neither hematological nor solid non-testis tumors) was observed in stage I seminoma patients treated with adjuvant carboplatin.

This study has several limitations. The first is that, although our database was maintained prospectively, this analysis was a retrospective, multicenter chart review of patients who were managed over a 15-year period and, thus, is subject to potential biases. Risk criteria for assigning patients to adjuvant chemotherapy varied between studies and length of follow-up is also different among them, which confers some heterogeneity. Another issue that needs to be considered when interpreting our results is the proportion of patients who were lost to follow-up. Because seminoma affects young men at the most mobile periods of their lives, it is not surprising that a significant proportion of our patients (19.8%) had <5 years of follow-up. Concern over the possibility that these men may have relapsed after they were lost to follow-up, thus, may have affected the results. However, this possibility is minimized by the fact that all men had >2 years of follow-up, a period in which most relapses occurred. A large randomized trial demonstrated that a single dose of carboplatin is equivalent to adjuvant irradiation for patients with stage I seminoma [19]. However, we decided to use two courses because only patients with risk factors we selected for adjuvant therapy. Furthermore, a dose–response relationship has been suggested for this drug in phase II and retrospective studies, resulting in a lower relapse rate with two (1.2%) versus one course (4.4%) [3].

The main obstacle to the wide implementation of this risk-adapted strategy is the absence of reliable prognostic factors for relapse. Several clinical and/or pathological features have been proposed in different series (tumor size, rete testis invasion, patient age, serum preochiectomy BHCG levels, invasion of blood or lymphatic vessels, pT staging), but none or a combination of them have been definitively validated [4, 9, 10, 15, 21, 22] (supplementary Table S4, available at *Annals of Oncology* online). However, most analyses were limited by its retrospective nature and often missing data in a significant proportion of reports. In our series, all these parameters were prospectively collected and artificial cut points on continuous variables were avoided. Although a central pathological review was not carried out, local pathologist were highly trained and motivated. Furthermore, this better represents daily clinical practice. We can now confirm the independent prognostic value of rete testis invasion and tumor size. The proposed new nomogram may be of help to oncologists for patient information and tailored management. Of course, this model needs prospective validation and testing in a different cohort of patients.

In conclusion, a risk-adapted approach is feasible for patients with stage I seminoma. Long-term results compare favorably with other established treatment options. Although the incidence of recurrences is significantly different, the pattern of relapses and outcomes are similar after adjuvant carboplatin than on active surveillance. A simple predictive model combining rete testis status and tumor size can estimate the individual probability of DFS and help to decide on the administration of adjuvant carboplatin therapy, thus eluding systematic (i.e. not individualized) treatment approaches. Future studies of molecular tumor characteristics or gene signatures and improved imaging techniques may help to define the best approach to the management of stage I seminoma.

disclosure

The authors have declared no conflict of interest.

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PD-L1 expression in nonclear-cell renal cell carcinoma

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Background: Programmed death ligand-1 (PD-L1) expression in nonclear-cell RCC (non-ccRCC) and its association with clinical outcomes are unknown.
Methods: Formalin-fixed paraffin-embedded (FFPE) specimens were obtained from 101 patients with non-ccRCC. PD-L1 expression was evaluated by immunohistochemistry in both tumor cell membrane and tumor-infiltrating mononuclear cells (TIMC). PD-L1 tumor positivity was defined as ≥5% tumor cell membrane staining. For PD-L1 expression in TIMC, a combined score based on the extent of infiltrate and percentage of positive cells was used. Baseline clinico-pathological characteristics and outcome data [time to recurrence (TTR) and overall survival (OS)] were correlated with PD-L1 staining.
Results: Among 101 patients, 11 (10.9%) were considered PD-L1+ in tumor cells: 2/36 (5.6%) of chromophobe RCC, 5/50 (10%) of papillary RCC, 3/10 (30%) of Xp11.2 translocation RCC and 1/5 (20%) of collecting duct carcinoma. PD-L1 positivity (PD-L1+) in tumor cells was significantly associated with higher stage ($P = 0.01$) and grade ($P = 0.03$), as well as shorter OS ($P < 0.001$). On the other hand, PD-L1 positivity by TIMC was observed in 57 (56.4%) patients: 13/36 (36.1%) of chromophobe RCC, 30/50 (60%) of papillary RCC, 9/10 (90%) of Xp11.2 translocation RCC and 5/5 (100%) of collecting duct carcinoma. A trend toward shorter OS was observed in patients with PD-L1+ in TIMC ($P = 0.08$). PD-L1+ in both tumor cell membrane and TIMC cells were associated with shorter TTR ($P = 0.02$ and $P = 0.03$, respectively).
Conclusion: In non-ccRCC, patients with PD-L1+ tumors appear to have worse clinical outcomes, although only PD-L1 positivity in tumor cells is associated with higher tumor stage and grade.
Key words: renal cell carcinoma, nonclear-cell renal cell carcinoma, benign kidney tumors, PD-L1, PD-1 inhibitors, immunotherapy

introduction

Renal cell carcinoma (RCC) has been widely recognized as a heterogeneous disease encompassing different histological subtypes [1]. Clear-cell RCC (ccRCC) is the most common subtype and accounts for more than 80% of the tumors that arise from the renal epithelium [2]. The remaining renal epithelial malignancies, collectively named as nonclear-cell RCC (non-ccRCC), include several subtypes such as papillary RCC (10%–15%), chromophobe RCC (5%), and the more rare forms, which include as Xp11.2 translocation RCC, unclassified RCC, and collecting duct carcinoma, among others [3].

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