Characterizing Sites of Metastasis in Metastatic Clear-Cell, Papillary and Chromophobe Renal-Cell Carcinoma

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Background

- There exists considerable biological and clinical variability between histologic variants of metastatic renal-cell carcinoma (mRCC).
- Data reporting on sites of metastatic involvement in less common histologies of mRCC are sparse.
- Sites of metastatic involvement are known to be associated with prognosis in mRCC and may reflect differences in underlying disease biology.
- We sought to characterize sites of metastasis and their association with survival across the three most common histologies of mRCC: clear-cell (ccRCC), papillary (pRCC), and chromophobe (chrRCC).

Methods

- Using the International mRCC Database Consortium (IMDC) database, patients with mRCC starting systemic therapy between 2002-2019 were identified and sites of metastasis at the time of first systemic therapy initiation were documented.
- Primary outcomes of interest were:
  - Prevalence of metastatic site involvement
  - Overall survival
- Patients with multiple sites of metastatic involvement were included in analyses of all groups to which they had metastases.
- Multivariable Cox regression models were performed to adjust for imbalances in IMDC risk factors.

Results

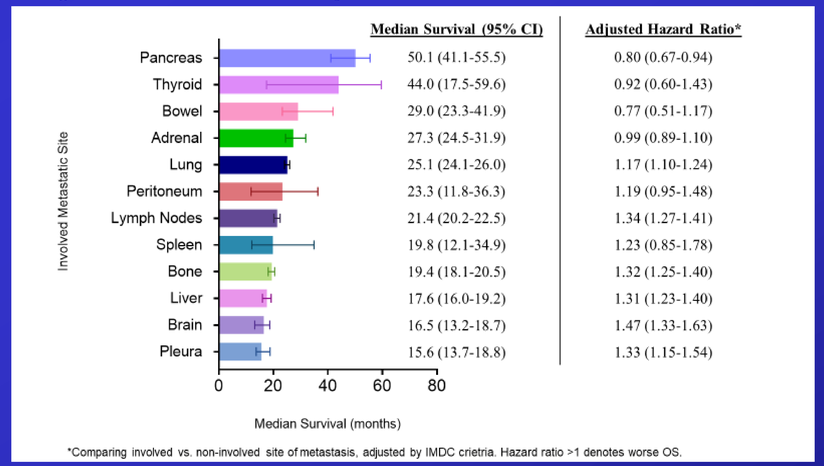
- A total of 10,105 patients were included in the analysis.
- Patient characteristics are reported in Table 1.
- Survival by site of metastatic involvement in ccRCC is shown is Figure 1.
- Sites of metastasis by histology are shown in Figure 2 and Table 2.

Table 1: Baseline Characteristics and IMDC Risk Factors

	Total (N=10,105)	ccRCC (N=9252)	pRCC (N=667)	chrRCC (N=186)	P-value*
Age, median (IQR)	60 (53-67)	60 (53-67)	61 (51-69)	58 (48-65)	<0.01
Sites of metastasis, median (range)	2 (0-7)	2 (0-7)	2 (0-6)	2 (0-4)	<0.01
Male	7310 / 10,104 (72%)	6712 / 9251 (73%)	497 / 667 (74%)	101 / 186 (54%)	<0.01
Sarcomatoid features	1034 / 8223 (13%)	944 / 7523 (13%)	53 / 524 (10%)	37 / 176 (21%)	<0.01
Nephrectomy	8526 / 10,094 (84%)	7809 / 9244 (84%)	545 / 664 (82%)	172 / 186 (92%)	<0.01
Region					<0.01
Asia	1180 / 10,105 (12%)	1072 / 9252 (12%)	93 / 667 (14%)	15 / 186 (8%)	
Europe	3515 / 10,105 (35%)	3299 / 9252 (36%)	162 / 667 (24%)	54 / 186 (29%)	
North America	5072 / 10,105 (50%)	4564 / 9252 (49%)	397 / 667 (60%)	111 / 186 (60%)	
Oceania	338 / 10,105 (3%)	317 / 9252 (3%)	15 / 667 (2%)	6 / 186 (3%)	
IMDC Risk Groups					<0.01
Favourable	1530 / 8153 (19%)	1422 / 7489 (19%)	71 / 514 (14%)	37 / 150 (25%)	
Intermediate	4621 / 8153 (57%)	4251 / 7489 (57%)	293 / 514 (57%)	77 / 150 (51%)	
Poor	2002 / 8153 (25%)	1816 / 7489 (24%)	150 / 514 (29%)	36 / 150 (24%)	

*Chi-squared test across all three groups

Figure 1: Overall Survival by Site of Metastatic Involvement in ccRCC



*Comparing involved vs. non-involved site of metastasis, adjusted by IMDC crietria. Hazard ratio >1 denotes worse OS.

Figure 2: Sites of Metastasis by Histology

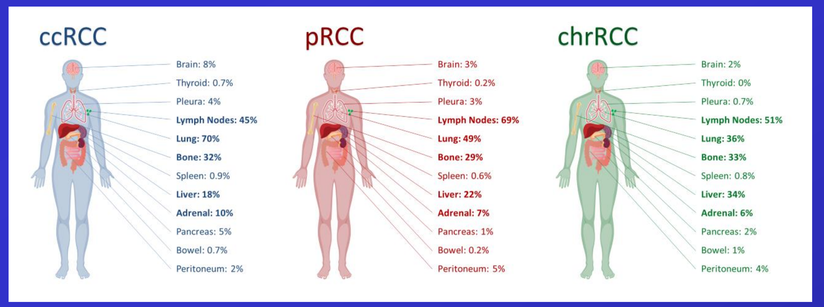


Table 2: Sites of Metastasis by Histology

Metastatic Site	ccRCC (N=9252)	pRCC (N=667)	chrRCC (N=186)	P-value*
Lung (95% CI)	70% (69-71)	49% (45-53)	36% (29-44)	<0.01
Lymph Nodes (95% CI)	45% (44-46)	69% (65-73)	51% (43-58)	<0.01
Bone (95% CI)	32% (31-33)	29% (26-33)	33% (27-41)	0.26
Liver (95% CI)	18% (17-19)	22% (19-26)	34% (28-41)	<0.01
Adrenal (95% CI)	10% (9-11)	7% (5-9)	6% (3-12)	0.02
Brain (95% CI)	8% (7-9)	3% (2-4)	2% (0.6-5)	<0.01
Pancreas (95% CI)	5% (5-6)	1% (0.6-3)	2% (0.5-6)	<0.01
Pleura (95% CI)	4% (4-5)	3% (2-5)	0.7% (0-4)	0.03
Peritoneum (95% CI)	2% (1.5-2.2)	5% (3-8)	4% (1-9)	<0.01
Spleen (95% CI)	0.9% (0.6-1.1)	0.6% (0.1-2)	0.8% (0-4)	0.88
Thyroid (95% CI)	0.7% (0.5-1.0)	0.2% (0-1)	0% (N/A)	0.25
Bowel (95% CI)	0.7% (0.5-0.9)	0.2% (0-1)	1.5% (0.2-5)	0.24

*Chi-squared test across all three groups

Conclusions

- Sites of metastatic involvement differ based on histology in mRCC and are associated with OS.
- These data highlight the clinical and biologic variability between histologic subtypes of mRCC.
- Patterns of metastatic spread may reflect differences in underlying disease biology.
- Further work to investigate differences in immune, molecular and genetic profiles between metastatic sites and histologic subtypes is encouraged.

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