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LA NEOPLASIA RENALE METASTATICA

Lucca, 02 Dicembre 2017

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Epidemiologia

Renal cell cancer represents 2-3% of all cancers, with the highest incidence in Western countries.

Due to increased detection of tumours by ultrasound (US) and computed tomography (CT), the number of incidentally diagnosed RCCs has increased (more than 50%).

25-30% of patients initially present with metastatic disease, while approximately 30% of patients who are treated for local RCC will relapse.

The classic triad of ***flank pain***, ***visible haematuria***, and ***palpable abdominal mass*** is rare (6-10%) and correlates with aggressive histology and advanced disease.

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs. Some symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough.

Siti di metastasi

Annals of Oncology 23: 973–980, 2012
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Distribution of metastatic sites in renal cell carcinoma: a population-based analysis

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One of the most widely cited studies of RCC metastasis distribution.

11,157 patients with mRCC were identified from 1998 to 2007.

Mean age was 64 years (median 64 years; IQR: 55–74 years). The majority were male (64%) and white (57%).

The most common sites of metastases were **lung** (45%), following by **bone** (30%) and **lymph node** (22%). **Liver** metastases were noted in 20% of patients and **adrenal** metastases were noted in 9% of patients. **Brain** and **pancreatic** metastases occurred in approximately 9% and 10% of patients.

The rate of single site metastases was 61% versus 39% for metastases at two or more sites.

Young age is inversely related to the number of site-specific metastases.

European Association of Urology

EUROPEAN UROLOGY 65 (2014) 577–584

Impact of Bone and Liver Metastases on Patients with Renal Cell Carcinoma Treated with Targeted Therapy

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Retrospective study

2027 patients of all ages with metastatic RCC who received first-line targeted therapy between 2003 and 2012

Patients with BMs had a significantly shorter median OS (14.9 vs 25.1 mo) and TTF (5.7 vs 7.6 mo than those without BMs.

Similarly, patients with LMs compared with those without LMs had a worse median OS (14.3 vs 22.2 mo) and TTF (5.5 vs 7.3 mo).

Table 2 – Univariate and multivariable analysis of bone metastases and liver metastases on overall survival and time-to-treatment failure

	OS			TTF		
	n	Median[a], mo	HR[b], 95% CI	*n*	Median[a], mo	HR[b], 95% CI
Model 1[c]						
Bone metastasis						
Yes	693	14.9	1.38 (1.22–1.56)	678	5.7	1.19 (1.07–1.33)
No	1334	25.1	Reference	1319	7.6	Reference
p value		<0.0001	<0.0001		<0.0001	0.001
Liver metastasis						
Yes	381	14.3	1.37 (1.18–1.58)	371	5.5	1.15 (1.01–1.32)
No	1646	22.2	Reference	1626	7.3	Reference
p value		<0.0001	<0.0001		0.013	0.032
Model 2[d]						
Bone and liver with or without other[e]	147	10.9	1.82 (1.47–2.26)	140	4.2	1.45 (1.19–1.78)
Bone with or without other[e]	546	16.2	1.40 (1.22–1.62)	538	6.4	1.16 (1.03–1.32)
Liver with or without other[e]	234	18.2	1.42 (1.17–1.73)	231	6.6	1.10 (0.93–1.30)
Other[e]	1100	27.1	Reference	1088	7.8	Reference
p value		<0.0001	<0.0001		<0.0001	0.001

CI = confidence interval; HR = hazard ratio; OS = overall survival; TTF = time-to-treatment failure.

[a] Log-rank test.

[b] Wald chi-square test from multivariable Cox regression adjusted for the International Metastatic Renal Cell Carcinoma Database Consortium risk factors, including time from diagnosis to treatment <1 yr, Karnofsky performance status <80%, hemoglobin less than the upper limit of normal, neutrophilia, thrombocytosis, and hypercalcemia.

[c] In model 1, bone metastases (BMs) (yes vs no) and liver metastases (LMs) (yes vs no) were evaluated as two individual factors.

[d] In model 2, patients were classified into four groups based on the combination of BMs and LMs (presence of both BMs and LMs, presence of either BMs or LMs, or other metastases).

[e] Other is defined as sites of metastasis excluding bone and liver.

Table 3 – Overall survival and time-to-treatment failure according to number and site of metastasis

	OS			TTF		
	n	Median[a], mo	HR[b], 95% CI	*n*	Median[a], mo	HR[b], 95% CI
Single metastasis	498			492		
Bone	72	16.8	1.18 (0.81–1.71)	70	8.1	1.08 (0.79–1.47)
Liver	25	16.4	1.06 (0.51–2.17)	25	7.2	1.09 (0.64–1.84)
Other[c]	401	32.6	Reference	397	8.3	Reference
Lung	256	33.7		254	8.6	
Lymph node	75	23.5		74	7.5	
Brain	5	-		5	–	
Other[d]	65	34.7		64	9.0	
p value		0.032	0.696		0.553	0.861
Two or more metastatic sites	1529			1505		
Bone and liver with or without other[c]	147	10.9	1.70 (1.36–2.12)	140	4.2	1.42 (1.15–1.74)
Bone and other[c]	474	16.1	1.38 (1.18–1.61)	468	6.1	1.16 (1.01-1.33)
Liver and other[c]	209	18.2	1.39 (1.14–1.71)	206	6.4	1.08 (0.90-1.30)
Other[c]	699	23.5	Reference	691	7.3	Reference
Lung	562	22.2		555	7.6	
Lymph node	410	19.0		407	6.6	
Brain	96	20.0		95	9.4	
Other[d]	349	26.0		346	7.8	
p value		<0.0001	<0.0001		<0.0001	0.006

CI = confidence interval; HR = hazard ratio; OS = overall survival; TTF = time-to-treatment failure.

[a] Log-rank test. Patients without bone metastases (BMs) and liver metastases (LMs) are combined as one group in the comparison (labeled as other[c]).

[b] Wald chi-square test from multivariable Cox regression adjusted for the IMDC risk factors, including time from diagnosis to treatment <1 yr, Karnofsky performance status <80%, hemoglobin less than the upper limit of normal, neutrophilia, thrombocytosis, and hypercalcemia. Patients without BMs and LMs are combined as one group in the comparison (labeled as other[c]).

[c] Other is defined as sites of metastasis excluding bone and liver.

[d] Other is defined as sites of metastasis excluding bone, liver, brain, lymph nodes, and lung.

Table 4 – Overall survival and time-to-treatment failure according to the International Metastatic Renal Cell Carcinoma Database Consortium risk groups and sites of metastasis

	Favorable		Intermediate		Poor	
	n	Median, mo	*n*	Median, mo	*n*	Median, mo
OS	321		969		504	
Bone and liver with or without other	16	15.8	58	11.2	58	7.4
Bone or liver with or without other	118	35.5	360	20.1	220	7.1
Other[a]	187	45.1	551	30.6	226	10.4
p value		0.016		<0.0001		0.005
TTF	320		960		497	
Bone and liver with or without other	16	5.0	57	5.3	55	3.1
Bone or liver with or without other	118	11.3	355	7.4	218	3.8
Other[a]	186	12.3	548	8.3	224	4.2
p value		0.073		0.009		0.100

OS = overall survival; TTF = time-to-treatment failure.
[a] Other is defined as sites of metastasis excluding bone and liver.

Table 6.4: Anatomical, histological, and clinical variables in the commonly used prognostic models for localised and metastatic RCC

Prognostic Models	Variables													
		TNM Stage	ECOG PS	Karnofsky PS	RCC related symptoms	Fuhrman grade	Tumour necrosis	Tumour size	Delay between diagnosis and treatment	LDH	Corrected calcium	Haemoglobin	Neutrophil count	Platelet count
Localised RCC	UISS	x	x			x								
	SSIGN	x				x	x	x						
	Post-operative Karakiewicz's nomogram	x			x	x		x						
Metastatic RCC	MSKCC prognostic system			x					x	x	x	x		
	IMDC			x	x						x	x	x	x
	Heng's model			x					x		x	x	x	x

ECOG-PS=Eastern Cooperative Oncology Group - performance status; IMDC=International Metastatic Renal Cancer Database Consortium; LDH=lactate dehydrogenase; MSKCC=Memorial Sloan Kettering Cancer Center; PS=performance status; SSIGN=Stage Size Grade Necrosis; UISS=University of California Los Angeles integrated staging system.

EAU Guidelines

BOX 57-6 Prognostic Factors for Renal Cell Carcinoma

CLINICAL
Performance status
Systemic symptoms
Symptomatic vs. incidental presentation
Anemia
Hypercalcemia
Elevated lactate dehydrogenase
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Thrombocytosis
Elevated alkaline phosphatase

ANATOMIC
Tumor size
Venous involvement
Extension into contiguous organs
Adrenal involvement (direct or metastatic)
Lymph node metastases
Distant metastases
Metastatic burden of disease

HISTOLOGIC
Nuclear grade
Histologic subtype
Presence of sarcomatoid features
Presence of histologic necrosis
Vascular invasion
Invasion of perinephric or renal sinus fat
Collecting system invasion
Surgical margin status

Modified from Lane BR, Kattan MW. Prognostic models and algorithms in renal cell carcinoma. Urol Clin North Am 2008;35:613–25.

Local therapy of metastatic RCC

Cytoreductive nephrectomy

Tumour resection is curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligo-metastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary.

Cytoreductive nephrectomy is currently recommended in ***mRCC patients with a good PS, large primary tumours and low metastatic volume***. In patients with poor PS or Metastatic Renal Cancer Database Consortium (IMDC) risk, small primaries and high metastatic volume and/or a sarcomatoid tumour, CN is not recommended.

EAU Guidelines

Local therapy of metastatic RCC

Lancet. 2001 Sep 22;358(9286):966-70.

Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial.

Mickisch GH[1], Garin A, van Poppel H, de Prijck L, Sylvester R; European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group.

J Urol. 2004 Mar;171(3):1071-6.

Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis.

Flanigan RC[1], Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED.

Two prospective randomized trials[1,2] with metastatic RCC showed that the addition of cytoreductive nephrectomy (CN) improves overall survival (OS) as compared to interferon-alpha (IFN-a) alone (13.6 months vs. 7.8 months; Hazard ratio=0.69, p=0.001).

IFN-a is a historic standard of care.

Patients were enrolled between 1991-1998.

Local therapy of metastatic RCC

Eur Urol. 2014 Oct;66(4):704-10. doi: 10.1016/j.eururo.2014.05.034. Epub 2014 Jun 13.

Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium.

Heng DY[1], Wells JC[2], Rini BI[3], Beuselinck B[4], Lee JL[5], Knox JJ[6], Bjarnason GA[7], Pal SK[8], Kollmannsberger CK[9], Yuasa T[10], Srinivas S[11], Donskov F[12], Bamias A[13], Wood LA[14], Ernst DS[15], Agarwal N[16], Vaishampayan UN[17], Rha SY[18], Kim JJ[19], Choueiri TK[20].

The benefit of cytoreductive nephrectomy (CN) for overall survival (OS) is unclear in patients with synchronous metastatic renal cell carcinoma (mRCC) in the era of targeted therapy.

Retrospective data from patients with synchronous mRCC (n=1658) from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) were used to compare 982 mRCC patients who had a CN with 676 mRCC patients who did not.

Patients who had CN had better IMDC prognostic profiles versus those without (favorable, intermediate, or poor in 9%, 63%, and 28% vs 1%, 45%, and 54%, respectively). The median OS of patients with CN versus without CN was 20.6 versus 9.5 mo ($p<0.0001$).

CN is beneficial in synchronous mRCC patients treated with targeted therapy, even after adjusting for prognostic factors. Patients with estimated survival times <12 mo or four or more IMDC prognostic factors may not benefit from CN.

Local therapy of metastatic RCC

J Urol. 2011 Jan;185(1):60-6. doi: 10.1016/j.juro.2010.09.012. Epub 2010 Nov 12.

The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy.

Choueiri TK[1], Xie W, Kollmannsberger C, North S, Knox JJ, Lampard JG, McDermott DF, Rini BI, Heng DY.

314 patients treated with anti-vascular endothelial growth factor.

On univariable analysis cytoreductive nephrectomy was associated with a median overall survival of 19.8 months compared to 9.4 months for patients who did not undergo cytoreductive nephrectomy (HR 0.44; 95% CI 0.32, 0.59; $p < 0.01$).

On multivariable analysis and adjusting for established prognostic risk factors the overall survival difference persisted (adjusted HR 0.68; 95% CI 0.46, 0.99; $p = 0.04$) in favor of the cytoreductive nephrectomy group.

In subgroup analyses stratified for favorable/intermediate/poor risk criteria, patients in the poor risk group had a marginal benefit ($p = 0.06$).

Local therapy of metastatic RCC

World J Urol. 2016 Dec;34(12):1651-1656. Epub 2016 Apr 15.

Minimally invasive cytoreductive nephrectomy: a multi-institutional experience.

Nunez Bragayrac L[1], Hoffmeyer J[2], Abbotoy D[3], Attwood K[4], Kauffman E[3], Spiess P[5], Wagner A[6], Schwaab T[3].

Retrospective study (to analyze the functional and oncologic outcomes of minimally invasive cytoreductive nephrectomy (CN) in three high-volume cancer centers.

120 patients underwent minimally invasive surgery (laparoscopic, hand-assisted laparoscopic, or robotic) partial or radical CN between May 2001 and May of 2013.

Most of the surgeries were radical (93.3 %) and performed laparoscopically (96.6 %).

Median operative time was 210 min, with a median estimated blood loss of 150 cc, and 11 (9.2 %) patients received blood transfusions.

Four (3.3 %) patients were converted to open surgery due to locally advanced disease and/or bleeding.

Minimally invasive cytoreductive nephrectomy is feasible and safe in experienced hands with acceptable morbidity and oncological outcomes.

Local therapy of metastatic RCC

Urol Oncol. 2017 Nov 8. pii: S1078-1439(17)30527-6. doi: 10.1016/j.urolonc.2017.09.030. [Epub ahead of print]

Trends in usage of cytoreductive partial nephrectomy and effect on overall survival in patients with metastatic renal cell carcinoma.

Lenis AT[1], Salmasi AH[1], Donin NM[1], Faiena I[1], Johnson DC[1], Drakaki A[2], Gollapudi K[3], Blumberg J[3], Belldegrun AS[4], Pantuck AJ[4], Chamie K[5].

Cytoreductive radical nephrectomy (cRN) improves survival in select patients with metastatic renal cell carcinoma (mRCC).

To compare overall survival (OS) in patients who underwent cRN or cPN for mRCC.

A total of 10,144 patients met inclusion criteria, with 9,764 (96.2%) undergoing cRN and 381 (3.8%) undergoing cPN.

cPN was associated with improved OS compared with cRN (log rank, P = 0.001). This effect was limited to primary tumors < 4cm.

The use of cPN in patients with mRCC is increasing. cPN is associated with improved OS in patients with mRCC, although this effect is limited to patients with primary tumors < 4cm.

Local therapy of metastatic RCC

Embolisation of the primary tumour

In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain.

Summary of evidence	LE
Cytoreductive nephrectomy combined with interferon-alpha improves survival in patients with metastatic RCC and good performance status.	1a
Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3

Recommendation	grade	
Offer cytoreductive nephrectomy to favourable- and intermediate-risk patients with metastatic RCC.	weak	↑

Local therapy of metastases in mRCC

Complete versus no/incomplete metastasectomy

Eight studies on RCC metastases in various organs compared complete vs. no and/or incomplete metastasectomy.

Six studies reported a significantly longer median OS or CSS following complete metastasectomy (the median value for OS or CSS was 40.75 months, range 23-122 months) compared with incomplete and/or no metastasectomy (the median value for OS or CSS was 14.8 months, range 8.4-55.5 months).

Of the two remaining studies, one showed no significant difference in CSS between complete and no metastasectomy, and one reported a longer median OS for metastasectomy albeit no p-value was provided.

Local therapy of metastases in mRCC

Cancer. 2011 Jul 1;117(13):2873-82. doi: 10.1002/cncr.25836. Epub 2011 Jan 10.

Survival after complete surgical resection of multiple metastases from renal cell carcinoma.

Alt AL[1], Boorjian SA, Lohse CM, Costello BA, Leibovich BC, Blute ML.

887 patients who underwent nephrectomy for RCC between 1976 and 2006 who developed multiple metastatic lesions.

Of 887 patients, 125 (14%) underwent complete surgical resection of all metastases.

Complete metastasectomy was associated with a significant prolongation of median cancer-specific survival (CSS) (4.8 years vs 1.3 years; $P < .001$).

Patients who had lung-only metastases had a 5-year CSS rate of 73.6% with complete resection versus 19% without complete resection ($P < .001$).

A survival advantage from complete metastasectomy also was observed among patients with multiple, nonlung-only metastases.

Complete resection of multiple RCC metastases may be associated with long-term survival.

Local therapy of metastases in mRCC

Local therapies for RCC bone metastases

Of the three studies identified, one compared single-dose image-guided radiotherapy (IGRT) with hypo-fractionated IGRT in patients with RCC bone metastases.

Int J Radiat Oncol Biol Phys. 2012 Apr 1;82(5):1744-8. doi: 10.1016/j.ijrobp.2011.02.040. Epub 2011 May 17.

Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma.

Zelefsky MJ[1], Greco C, Motzer R, Magsanoc JM, Pei X, Lovelock M, Mechalakos J, Zatcky J, Fuks Z, Yamada Y.

Single-dose IGRT (> 24 Gray) had a significantly better three-year actuarial local PFS rate, also shown by Cox regression analysis.

Local therapy of metastases in mRCC

Local therapies for RCC bone metastases

A study compared the efficacy and durability of pain relief between single-dose stereotactic body radiotherapy (SBRT) and conventional radiotherapy (CRT) in patients with RCC bone metastases to the spine.

Pract Radiat Oncol. 2012 Oct-Dec;2(4):e95-e100. doi: 10.1016/j.prro.2012.01.005. Epub 2012 Feb 15.

The efficacy of external beam radiotherapy and stereotactic body radiotherapy for painful spinal metastases from renal cell carcinoma.

Hunter GK[1], Balagamwala EH[1], Koyfman SA[1], Bledsoe T[1], Sheplan LJ[1], Reddy CA[1], Chao ST[1], Djemil T[1], Angelov L[2], Videtic GM[3].

Pain, objective response rate (ORR), time-to-pain relief and duration of pain relief were similar.

Local therapy of metastases in mRCC

Local therapies for RCC brain metastases

Two studies on RCC brain metastases were included. A three-armed study compared stereotactic radiosurgery (SRS) vs. whole brain radiotherapy (WBRT) vs. SRS + WBRT.

Strahlenther Onkol. 2010 Apr;186(4):210-7. doi: 10.1007/s00066-010-2055-z. Epub 2010 Feb 22.

Radiotherapy for brain metastases from renal cell cancer: should whole-brain radiotherapy be added to stereotactic radiosurgery?: analysis of 88 patients.

Fokas E[1], Henzel M, Hamm K, Surber G, Kleinert G, Engenhart-Cabillic R.

Two-year OS and intracerebral control were equivalent in patients treated with SRS alone and SRS + WBRT.

Both treatments were superior to WBRT alone in the general study.

Local therapy of metastases in mRCC

Local therapies for RCC brain metastases

The other study compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy (MTS) + CRT or CRT alone.

Int J Radiat Oncol Biol Phys. 2000 Dec 1;48(5):1389-93.

Fractionated stereotactic radiotherapy of brain metastases from renal cell carcinoma.

Ikushima H[1], Tokuuye K, Sumi M, Kagami Y, Murayama S, Ikeda H, Tanaka M, Oyama H, Shibui S, Nomura K.

One-, two- and three-year survival rates were higher but not significantly so for FSRT as for metastasectomy + CRT, or CRT alone.

Fractionated stereotactic radiotherapy did not result in a significantly better two-year local control rate compared with MTS + CRT.

Local therapy of metastases in mRCC

Embolisation of metastases

Embolisation prior to resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms.

7.3.2.5. Summary of evidence and recommendations for local therapy of metastases in metastatic RCC

Summary of evidence	**LE**
All included studies were retrospective non-randomised comparative studies, resulting in a high risk of bias associated with non-randomisation, attrition, and selective reporting.	3
With the exception of brain and possibly bone metastases, metastasectomy remains by default the only local treatment for most sites.	3
Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of overall survival, cancer-specific survival and delay of systemic therapy.	3
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).	3

Recommendations	**grade**	
Consider local therapy for metastatic disease (including metastasectomy) in patients with a favourable risk profile in whom complete resection is achievable or when local symptoms need to be controlled.	weak	↑
Stereotactic radiotherapy for clinically relevant bone or brain metastases can be considered for local control and symptom relief.	weak	↑

GRAZIE PER L'ATTENZIONE