Surgical decision-making for long bone metastases

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CHAPTER 9

Metastasectomy, Intralesional Resection, Or Stabilization Only In The Treatment Of Bone Metastases From Renal Cell Carcinoma

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ABSTRACT

Objectives

To assess differences in: (1) local tumor recurrence, (2) reoperation, and (3) survival between metastasectomy, intralesional curettage, and stabilization only for renal cell carcinoma metastases to the appendicular skeleton. Secondarily, we evaluated whether there is a difference in these outcomes based on tumor margin status.

Design

Retrospective cohort study.

Setting

Two tertiary care referral centers for orthopaedic oncology.

Participants

183 consecutive patients with renal cell carcinoma bone metastasis in the appendicular skeleton who underwent surgery between 1990 and 2015.

Interventions

Metastasectomy (48%, n=88, margins: 64 negative; 20 positive; 4 unclear), intralesional curettage (30%, n=54), and stabilization only (22%, n=41).

Outcome measures

Local recurrence, reoperation, and survival.

Results

The recurrence rate differed and was highest after stabilization only (39%), followed by intralesional curettage (22%), and metastasectomy (12%) ($p = 0.003$). However, we found no difference in reoperation rate ($p = 0.847$). Survival was better in patients who underwent metastasectomy ($p = 0.020$). The recurrence rate was lower in patients who had a negative margin (5%) as compared to those with a positive margin (26%) ($p < 0.001$). However, we found no difference in reoperation rate ($p = 0.97$). Negative margins showed better survival ($p < 0.001$).

Conclusions

Our findings emphasize the importance of obtaining negative margins in patients with a good life expectancy, as lower recurrence rate can be attained at a comparable risk for reoperation, with a potential impact on survival.

INTRODUCTION

Renal cell carcinoma (RCC) bone metastases are often hypervascular and relatively radioresistant.[1] Patients have a favorable prognosis as compared to patients with other primary tumors; their overall one-year survival rate ranges from 47% to 88%.[2-5] RCC bone metastases are challenging to treat given their radioresistant nature. The mainstay of treatment is surgery with indications for surgical intervention ranging from a pathological fracture, through a lesion at risk of fracture, to a solitary lesion.[6] Surgical techniques are usually grouped into metastasectomy, intralesional treatment, and stabilization only.[7,8] Factors considered in the decision to operate and the selection of surgical strategy include: location and size of the lesion, oncologic burden (i.e. visceral and other bone metastases), presence of a fracture, and life expectancy.[9,10]

It is unclear how oncological outcome –survival and tumor recurrence– are affected by these different surgical strategies. Several studies suggest improved survival after metastasectomy as compared to patients who underwent intralesional treatment; however, these findings are not confirmed by others.[4,7,8,11] Tumor recurrence and subsequent reoperations are less commonly described and compared between surgical strategies.[8,12]

We aim to compare different surgical techniques for renal cell carcinoma bone metastases. Specifically, we assessed differences in: (1) local tumor recurrence, (2) reoperation, and (3) survival between metastasectomy, intralesional curettage, and stabilization only for renal cell carcinoma metastasis to the appendicular skeleton. Secondarily, we evaluated whether there is a difference in these outcomes based on tumor margin status.

METHODS

Study Design

Our institutional review board approved this retrospective study. We used our orthopaedic oncology database including data on all patients with musculoskeletal tumors from two tertiary care referral centers for orthopaedic oncology and queried pathology and operative reports using a combination of the words “renal cell carcinoma” and “bone” and “metastases”, including synonyms and misspellings between January 1990 and January 2015. We identified 864 patients. We reviewed the medical records of all identified patients and included patients 18 years of age and older who underwent surgical treatment for a renal cell metastasis in the appendicular skeleton. Exclusion criteria were revision surgery and biopsies. We only included the first surgery per patient so as to not violate the assumption of independence.[13] All remaining 183 eligible patients were included. We included all patients, regardless of followup duration, and accounted for this in our statistical analyses.

Surgical Strategies

The surgeon decided together with the patient on the need for surgery and the surgical strategy. Eighty patients (44%) were treated in hospital 1 and 103 (56%) in hospital 2. One hundred seventy-four (95%) of the 183 surgeries were performed by 10 orthopaedic oncologists; the remainder by trauma surgeons.

We divided the surgical approach into: metastasectomy, intralesional curettage, and stabilization only. In general, a higher proportion of patients with a solitary metastasis or less disseminated disease –resulting in a relatively good prognosis and low metastatic load– underwent metastasectomy. These procedures were not limited by the location of the tumor; enbloc resections were performed in the extremities, the shoulder girdle, and the pelvis. An endoprosthetic reconstruction was almost always performed after resection; however, in some pelvic and scapular lesions, reconstruction was not deemed necessary (Appendix 1). Postoperative radiation therapy was not routinely performed after metastasectomy. Stabilization by intramedullary nailing or open reduction and internal fixation using plate and screws with or without intralesional curettage and cement packing was more commonly done in patients with a worse prognosis and higher oncologic burden. Patients receiving intralesional curettage with subsequent fixation with plates and screws or intramedullary nail devices, and patients whom received surgical stabilization only, were more often treated with postoperative radiation.

There was heterogeneity in postoperative care between patients due to differences in the degree of illness.

Outcome Measures

Our outcome measures were (1) local tumor recurrence/progression, (2) reoperation, and (3) survival. Local recurrence was defined as identification of metastasis in radiographs or CT scan after resection with negative margins or resection with positive margins (intralesional curettage and enbloc resections with positive margins).[14] Tumor progression, grouped with local tumor recurrence, was defined as identification of metastasis increasing in size in radiographs or CT scan in patients receiving surgical stabilization only.[14] A patient with no signs of recurrence or progression at the last imaging was considered censored, meaning that the outcome did not occur by the last moment of followup. Reoperations were identified by two research fellows (D.L., Q.v.d.V.) who independently checked all reports of surgeries performed after the index procedure. A patient who did not undergo a reoperation before the last moment of clinical followup was considered censored. Survival was defined as the period between the date of surgery and date of death. We used the Social Security Death Index to determine the date of death; March 18th 2015 was the final moment of followup to establish the date of death.[15] We only considered the first notice of local recurrence and reoperation in our time-to-event analyses. Fourteen (8%) patients had no followup imaging and were not included in the analysis of local recurrence, 1 (0.5%)

patient had no clinical followup and was not included in the reoperation analysis, and all patients had complete followup for date of death.

We obtained data on the following explanatory variables through chart review of electronic medical records by two research fellows (D.L., Q.v.d.V.): age, sex, body mass index, smoking status, preoperative hemoglobin level (in g/dL), preoperative white blood cell count (in K/uL), preoperative albumin level (in g/dL), preoperative calcium level (in mg/dL), histological subtype, time diagnosis primary tumor until surgery, time first notice of a metastasis until surgery, presence of a solitary metastasis, presence of visceral metastases, presence of multiple bone metastases, Eastern Cooperative Oncology Group (ECOG) performance status, modified Charlson Comorbidity Index, additional comorbidities, previous systemic therapy, previous conventional radiation, postoperative conventional radiation within two months, anesthesia type, preoperative embolization, anatomic location of surgery, presence of a pathological fracture, surgical strategy, implant type, cement use during surgery, margin status, estimated blood loss, duration of surgery, length of hospital stay, reason for reoperation, type of reoperation, and last date of followup.

The surgical technique, anatomic location of surgery, and the implant type were derived from operative reports (Appendix 1). The surgical strategy to remove the tumor was divided into: metastasectomy, intralesional curettage, and stabilization only. Metastasectomy was defined as an intended enbloc resection with or without reconstruction.[6] Intralesional curettage with cement packing was often combined with intramedullary nailing or open reduction and internal fixation with plate and screws. Stabilization only was almost always done using an intramedullary nail.

9

Pathology reports were reviewed to assess the margin status, which was considered to be positive in case of any residual tumor after enbloc resection. Margins were also considered positive in all intralesional curettage and stabilization only patients.[4] We also reviewed the pathology reports to assess the histological subtype of the tumor lesion. Tumor margin was not reported for four (2%) patients, we did not include these in our analysis.

The Eastern Cooperative Oncology Group (ECOG) performance status was retrieved from chart review. This instrument describes a patient level of function ranging from fully active (0) to completely disabled (4). We dichotomized this into two groups: 0-1-2 and 3-4.

An algorithm based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes was used to calculate the Modified Charlson Comorbidity Index score at the time of the index surgery (Appendix 2).[16] The index ranges from 0 to 24 with a higher score indicating more severe comorbidity status. Additional comorbidity was defined as a patient who had any of the comorbidities in addition to the metastatic tumor.

We compared outcomes between patients who underwent metastasectomy, intralesional curettage, and stabilization only. We also compared outcomes between patients with a negative (enbloc resection with negative margin) and positive margin (intralesional curettage, stabilization only, and enbloc resection with positive margins).

We did four additional subanalyses: assessing survival based on resection type and margin status in patients with a solitary metastases only (24% [44/183]), and survival based on resection type and margin status in patients with multiple –visceral or bone– metastases (76% [139/183]).

Followup

The median followup was 10 months (interquartile range: 2 to 26 months, range 0 months to 17 years). One hundred fourteen (62%) patients were alive at clinical followup after 6 months, 62 (34%) were deceased and 7 (4%) were lost to followup. After 12 months: 84 (46%) patients were still in clinical followup, 87 (48%) were deceased, and 12 (7%) were lost to followup. Two years after surgery, 49 (27%) were still in clinical followup, 112 (61%) were deceased, and 22 (12%) were lost to followup. Five years after surgery, 10 (5%) were still in clinical followup, 137 (75%) were deceased, and 36 (20%) were lost to followup.

Statistical Analysis

We presented continuous variables as a mean with standard deviation (SD) and categorical variables as frequencies with percentages.

Baseline characteristics were compared in bivariate analysis to assess differences between the group of patients who underwent metastasectomy, intralesional curettage, and stabilization only. We used a Fisher exact test for categorical variables and a one-way analysis of variance (ANOVA) for continuous variables.

We used log-rank analysis to compare local tumor recurrence, reoperation, and survival between the three groups. We used Kaplan-Meier plots to demonstrate the outcomes over time and calculate one-year and five-year probabilities with 95% confidence intervals (95% CI). Visual inspection of log-log plots suggest no violation of the proportional hazards assumption.[17]

All statistical analyses were performed using Stata® 13.0 (StataCorp LP, College Station, TX, USA). A two-tailed *p* value less than 0.05 was considered statistically significant.

There were missing values for some variables (Table 1); these were not included in the respective analyses.

RESULTS

Baseline Characteristics

One-hundred and twenty-seven patients were men (69%); the overall mean age was 65 years (SD 10) (Table 1). Eighty patients (44%) had a pathological fracture and 103 patients (56%) had an impending fracture. Eighty-eight (48%) patients underwent a metastasectomy, 54 (30%) underwent intralesional curettage, and 41 (22%) had stabilization only. Of the

88 patients who underwent metastasectomy; 64 (73%) had negative margins, 20 (23%) had positive margins, and margin status was unclear in four. The majority had a clear cell histological subtype (86% [140/163]), and the histological subtype was unknown in 20 (11%) patients. The mean estimated blood loss –available in 163 patients– was 772 mL (SD: 1199 mL), the mean length of hospital stay –available in 177 patients– was 7.3 days (SD: 6.0 days).

When comparing baseline characteristics between groups we found that (Table 2): visceral metastases were more common in the intralesional curettage group (70%) and stabilization only group (71%) as compared to the metastasectomy group (42%) (p = 0.001); multiple bone metastases were most common in the stabilization only group (73%), and less common in the intralesional curettage (48%) and metastasectomy group (47%) (p = 0.012). This results in a higher proportion of patients with solitary metastasis (34%) in the metastasectomy group as compared to the other groups (p = 0.001). Postoperative radiation within two months (p < 0.001) was more commonly done after stabilization only and intralesional curettage. Cement was predominantly used in the intralesional curettage and metastasectomy groups (p < 0.001). The type of reconstruction also varied between the groups; endoprosthetic reconstruction was the most common after metastasectomy, open reduction internal fixation after intralesional curettage, and intramedullary nailing after stabilization only (p < 0.001).

Table 1: Baseline characteristics

	n = 183
Patient characteristics	**Mean (±Standard deviation)**
Age (in years)	65 ± 10
Body mass index* (in kg/m^2)	29 ± 7.1
Modified Charlson Comorbidity Index	6.7 ±1.5
Time since primary tumor diagnosis (in days)*	1306 ± 1641
Time since diagnosis of metastasis (in days)*	463 ± 889
Hemoglobin (in g/dL)*	11 ± 1.9
White blood cell count (in K/uL)*	9.9 ± 4.7
Albumin (in g/dL)*	3.8 ± 0.6
Calcium (in mg/dL)*	8.9 ± 0.8
	n (%)
Men	127 (69)
Smoking*	
Never smoked	45 (30)
Quit > 1 year ago	82 (55)
Current smoker	23 (15)
Additional comorbidity	59 (33)

Table 1: Baseline characteristics (*continued*)

	Mean (±Standard deviation)
Eastern Cooperative Oncology Group Performance status*	
0 - 2	98 (92)
3 - 4	9 (8)
Tumor characteristics	**n (%)**
Pathological fracture	80 (44)
Solitary metastasis	44 (24)
Visceral metastases	
None	77 (42)
Lung/liver	82 (45)
Brain	6 (3)
Lung/liver and brain	18 (10)
Multiple bone metastases	97 (53)
Histology*	
Clear cell	140 (86)
Non clear cell*	23 (14)
Treatment characteristics	n (%)
Operation	
Endoprosthetic reconstruction	70 (38)
Intramedullary nailing	52 (28)
Open reduction internal fixation	39 (21)
Resection/curretage only	22 (12)
Type of resection	
Metastasectomy (En bloc resection)	88 (48)
Intralesional curettage	54 (30)
Stabilization only	41 (22)
Cement use	101 (55)
Negative margins	65 (36)
Previous local radiotherapy	50 (27)
Postoperative radiotherapy within two months	49 (27)
Previous systemic therapy	56 (31)
Preoperative embolization	87 (48)

Body mass index was available in 111 (61%) cases, modified Charlson Comorbidity Index in 181 (99%), time since primary tumor diagnosis in 179 (98%), time since diagnosis of metastasis in 177 (97%), hemoglobin in 178 (97%), white blood cell count in 179 (98%), albumin in 100 (55%), calcium in 167 (91%), smoking in 150 (81%), Eastern Cooperative Oncology Group Performance Status in 107 (58), histology in 163 (89)
(Non clear cell histology: Sacromatoid (7), clear cell + sarcomatoid (5) clear
cell + granular (2), poorly differentiated (2), chromophobe (1), adenocarcinoma (1), clear cell + papillary + oxyphilic (1), clear cell + papillary + rhabdoid (1), clear cell + sarcomatoid + papillary (1), granular (1), sarcomatoid + unclassified (1)

Table 2: Bivariate analyses

				n = 183
	Metastasectomy (n = 88)	**Intralesional curettage (n = 54)**	**Stabilization only (n = 41)**	***p* value**
Patient characteristics	**Mean (±Standard deviation)**	**Mean (±Standard deviation)**	**Mean (±Standard deviation)**	
Age (in years)	63 ±10	66 ±11	67 ±10	*0.203*
Body mass index (in kg/m^2)*	29 ±7.9	31 ±6.5	29 ±6.2	*0.305*
Modified Charlson Comorbidity Index*	6.6 ±1.4	6.6 ±1.6	6.9 ±1.3	*0.482*
Time since primary tumor diagnosis (in days)*	1479 ±1757	1014 ±1265	1324 ±1798	*0.270*
Time since diagnosis of metastasis (in days)*	432 ±840	449 ±800	548 ±1095	*0.788*
Hemoglobin (in g/dL)*	11 ±2.0	12 ±1.8	12 ±1.9	*0.068*
White blood cell count (in K/uL)*	10 ±4.4	10 ±5.6	9 ±3.7	*0.376*
Albumin (in g/dL)*	3.9 ±0.59	3.8 ±0.57	3.7 ±0.62	*0.423*
Calcium (in mg/dL)*	8.9 ±0.82	8.9 ±0.86	8.9 ±0.69	*0.919*
	n (%)	**n (%)**	**n (%)**	
Men	62 (70)	39 (72)	26 (63)	*0.623*
Smoking*				
Never smoked	24 (36)	12 (27)	9 (23)	
Quit > 1 year ago	36 (54)	20 (45)	26 (67)	*0.083*
Current smoker	7 (10)	12 (27)	4 (10)	
Additional comorbidity	27 (31)	15 (29)	17 (41)	*0.393*
Eastern Cooperative Oncology Group Performance status*				
0 - 2	40 (93)	29 (85)	29 (97)	*0.276*
3 - 4	3 (7)	5 (14)	1 (3)	
Tumor characteristics	n (%)	n (%)	n (%)	
Pathological fracture	40 (45)	24 (44)	16 (39)	*0.821*
Solitary metastasis	30 (34)	12 (22)	2 (5)	***0.001***
Visceral metastases	37 (42)	38 (70)	29 (71)	***0.001***
Multiple bone metastases	41 (47)	26 (48)	30 (73)	***0.012***
Histology*				
Clear cell	65 (83)	41 (87)	34 (89)	*0.706*
Non clear cell	13 (17)	6 (13)	4 (11)	
Treatment characteristics	**n (%)**			
Operation				
Endoprosthetic reconstruction	61 (69)	9 (17)	0 (0)	
Intramedullary nailing	0	13 (24)	39 (95)	***<0.001***
Open reduction and internal fixation	13 (15)	24 (44)	2 (5)	
Resection/curettage	14 (16)	8 (15)	0 (0)	

Table 2: Bivariate analyses (*continued*)

	Metastasectomy (n = 88)	Intralesional curettage (n = 54)	Stabilization only (n = 41)	*p* value
Cement use	57 (65)	43 (80)	1 (2)	***<0.001***
Previous local radiotherapy	29 (33)	13 (24)	8 (20)	*0.255*
Postoperative radiotherapy within two months	7 (8)	18 (33)	24 (59)	***<0.001***
Previous systemic therapy	25 (28)	18 (33)	13 (32)	*0.817*
Preoperative embolization	49 (56)	22 (41)	16 (39)	*0.109*

Body mass index was available in 111 (61%) cases, modified Charlson Comorbidity Index in 181 (99%), time since primary tumor diagnosis in 179 (98%), time since diagnosis of metastasis in 177 (97%), hemoglobin in 178 (97%), white blood cell count in 179 (98%), albumin in 100 (55%), calcium in 167 (91%), smoking in 150 (82%), Eastern Cooperative Oncology Group Performance Status in 107 (58), histology in 163 (89) (Non clear cell histology: sarcomatoid (7), clear cell + sarcomatoid (5) clear cell + granular (2), chromophobe (1), adenocarcinoma (1), clear cell + papillary + oxyphilic (1), clear cell + papillary + rhabdoid (1), clear cell + sarcomatoid + papillary (1), granular (1), poorly differentiated (1), sarcomatoid + unclassified (1). **Bold** indicates significant difference (two-tailed *p* value below 0.05).

Local Tumor Recurrence, Reoperation, And Survival Between Treatment Groups

The local recurrence rate varied between groups and was highest after stabilization only (39%, [15/38]), followed by intralesional curettage (22%, [11/50]), and metastasectomy (12%, [10/81]) (p = 0.003) (Figure 1). The oneyear local recurrence probability was 0.13 (95% CI: 0.06 to 0.26) after metastasectomy, 0.32 (95% CI: 0.17 to 0.55) after intralesional curettage, and 0.20 (95% CI: 0.09 to 0.42) after stabilization only. The five-year local recurrence probability was 0.26 (95% CI: 0.14 to 0.44) after metastasectomy, 0.77 (95% CI: 0.40 to 0.98) after intralesional curettage, and 0.85 (95% CI: 0.63 to 0.97) after stabilization only.

However, we found no difference, with the numbers evaluated, in overall reoperation rate between the metastasectomy (19%, [17/88]), intralesional curettage (19%, [10/53]), and surgical stabilization groups (17%, [7/41]) (p = 0.847) (Figure 2). The one-year reoperation probability was 0.21 (95% CI: 0.12 to 0.34) after metastasectomy, 0.16 (95% CI: 0.06 to 0.32) after intralesional curettage, and 0.07 (95% CI: 0.02 to 0.27) after stabilization only. The five-year reoperation probability was 0.32 (95% CI: 0.21 to 0.48) after metastasectomy, 0.63 (95% CI: 0.41 to 0.93) after intralesional curettage, and 0.47 (95% CI: 0.26 to 0.87) after stabilization only. The overall most common reasons for reoperation were: recurrence (11%, [20/182]) and deep infection (4.9%, [9/182]). After metastasectomy 6.8% (6/88) had a reoperation for a deep infection and 6.8% (6/88) for recurrence, while the rates were 15% (8/53) for recurrence and 5.7% (3/53) for deep infection after intralesional curettage, and 15% (6/41) for recurrence in the stabilization only group without any deep infection described (Table 3).

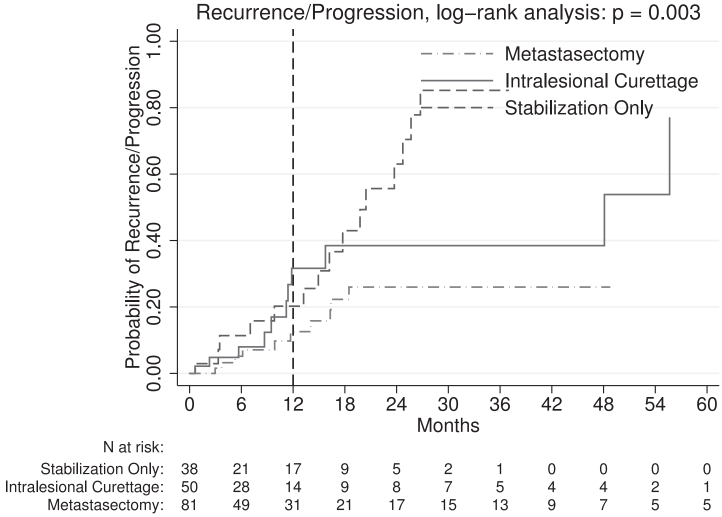

Figure 1: Local recurrence probability in the metastasectomy group (dashed dot line), intralesional curettage group (solid line), and stabilization only group (dashed line) are shown.

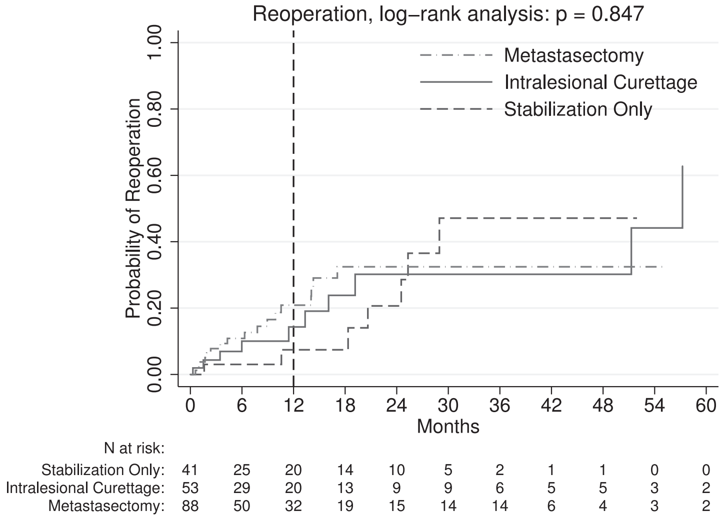

Figure 2: Reoperation probability in the metastasectomy group (dashed dot line), intralesional curettage group (solid line), and stabilization only group (dashed line) are shown.

Survival was better in patients who underwent metastasectomy as compared with those who underwent intralesional curettage or stabilization only (p = 0.020) (Figure 3). However, when we focused on patients with solitary bone metastases (24%, [44/183]) we found no difference, with the numbers evaluated, in survival between treatment groups (p = 0.997). Focusing on patients with multiple metastases (76%, [139/183]) we also found no difference in survival comparing the different surgical techniques (p = 0.099).

Table 3: Reason for reoperation and surgical strategy

Sex, Age	Path. fract.	Histology	Anatomic location	Type of surgery	Implant	Reason for reoperation	Months, reoperation
F, 71	No	CC	Acetabulum	Intralesional curettage	ORIF	Deep infection	0, ID
M, 70	No	CC	Ulna/ metacarpal	Intralesional curettage	ORIF	Deep infection	1, ID
F, 46	No	CC	Tibia	Intralesional curettage	Curettage only	Pain and recurrence	3, Tumor resection, MTP - knee + cement
M, 72	No	CC	Pelvis	Intralesional curettage	Curettage only	Recurrence	13, Resection soft tissue recurrence
M, 62	No	CC	Femur	Intralesional curettage	ORIF	Recurrence	16, Revision curettage, new plate-screw fixation + cement
M, 67	Yes	NCC	Humerus	Intralesional curettage	ORIF	Recurrence	19, Tumor resection, new plate-screw fixation + cement
M, 69	No	CC	Femur	Intralesional curettage	ORIF	Recurrence	52, Revision curettage, new plate-screw fixation + cement
M, 72	Yes	CC	Humerus	Intralesional curettage	IMN	Recurrence	58, Tumor resection, nail removal, hemia long-stem (shoulder)
M, 49	No	CC	Humerus	Intralesional curettage	Curettage only	Recurrence	6, Tumor resection + osteoarticular allograft and plate
M, 72	Yes	CC	Tibia	Intralesional curettage	IMN	Recurrence & deep infection	11, ID, tumor resection, AB impregnated spacer
M, 63	No	CC	Femur	Stabilization only	IMN	Peri-implant fracture	1, Refixation nail
M, 61	Yes	CC	Humerus	Stabilization only	IMN	Recurrence	10, Tumor resection, nail removal, MTP shoulder
M, 55	No	CC	Femur	Stabilization only	IMN	Recurrence	18, Tumor resection, THA
M, 65	Yes	CC	Humerus	Stabilization only	IMN	Recurrence	20, Tumor resection, nail removal, intercalary allograft + new nail
M, 48	Yes	CC	Humerus	Stabilization only	IMN	Recurrence	24, Tumor resection, nail removal, intercalary prosthesis + cement
M, 63	Yes	CC	Femur	Stabilization only	IMN	Recurrence	25, Tumor resection, nail removal, MTP - with cup (hip)
M, 67	No	CC	Femur	Stabilization only	IMN	Recurrence	29, Tumor resection, total femur replacement (hinge knee + bipolar hip)
M, 44	No	CC	Femur	Metastasectomy	ORIF	Allograft fracture	6, Revision ORIF
M, 57	Yes	CC	Humerus	Metastasectomy	ORIF	Allograft nonunion	14, Removal allograft, new allograft with hemia long-stem (shoulder)

Table 3: Reason for reoperation and surgical strategy (*continued*)

Sex, Age	Path. fract.	Histology	Anatomic location	Type of surgery	Implant	Reason for reoperation	Months, reoperation
M, 76	Yes	CC	Femur	Metastasectomy	EPR	Deep infection	1, ID
M, 70	Yes	CC	Femur	Metastasectomy	EPR	Deep infection	1, ID
F, 67	No	CC	Pelvis	Metastasectomy	ORIF	Deep infection	1, ID
M, 63	Yes	CC	Humerus	Metastasectomy	EPR	Deep infection	2, ID + head exchange
F, 86	No	CC	Pelvis	Metastasectomy	Resection only	Deep infection	4, ID
F, 54	No	CC	Tibia	Metastasectomy	EPR	Deep infection	7, ID
F, 55	No	CC	Pelvis	Metastasectomy	EPR	Dislocation	1, Open reduction
M, 57	No	CC	Femur	Metastasectomy	EPR	Loosening prosthesis	3, Revision femoral component
M, 79	Yes	CC	Humerus	Metastasectomy	ORIF	Loss of distal fixation	0, Revision plate fixation
M, 63	No	CC	Scapula	Metastasectomy	Resection only	Recurrence	10, Resection soft tissue recurrence
M, 71	Yes	NCC	Tibia	Metastasectomy	ORIF	Recurrence	14, Knee disarticulation
F, 53	No	CC	Pelvis	Metastasectomy	Resection only	Recurrence	14, Tumor resection hemipelvis
F, 54	Yes	CC	Humerus	Metastasectomy	ORIF	Recurrence	17, Removal allograft, tumor resection, new allograft + orif
M, 55	Yes	CC	Humerus	Metastasectomy	EPR	Recurrence	9, Above elbow amputation
F, 50	No	NCC	Femur/ acetabulum	Metastasectomy	EPR	Recurrence & dislocation	10, Open reduction

IMN = intramedullary nailing, EPR = endoprosthetic replacement, ORIF = open reduction and internal fixation, MTP = modular total prosthesis, ID = Incision & Debridement. Path. Fract. = Pathological fracture, CC = Clear cell, NCC = Non clear cell

Local Tumor Recurrence, Reoperation, And Survival Based On Margin Status

The local recurrence rate was lower in patients who had a negative margin as compared to those with a positive margin ($p < 0.001$) (Figure 4). The one-year recurrence probability was 0.03 (95% CI: 0.00 to 0.21) when a patient had negative margins and 0.25 (95% CI: 0.16 to 0.39) when a patient had positive margins. The five-year recurrence probability was 0.11 (95% CI: 0.04 to 0.31) when a patient had negative margins and 0.87 (95% CI: 0.60 to 0.99) when a patient had positive margins.

However, we found no difference in overall reoperation rate between patients who had a negative margin as compared to those with a positive margin ($p = 0.975$) (Figure 5).

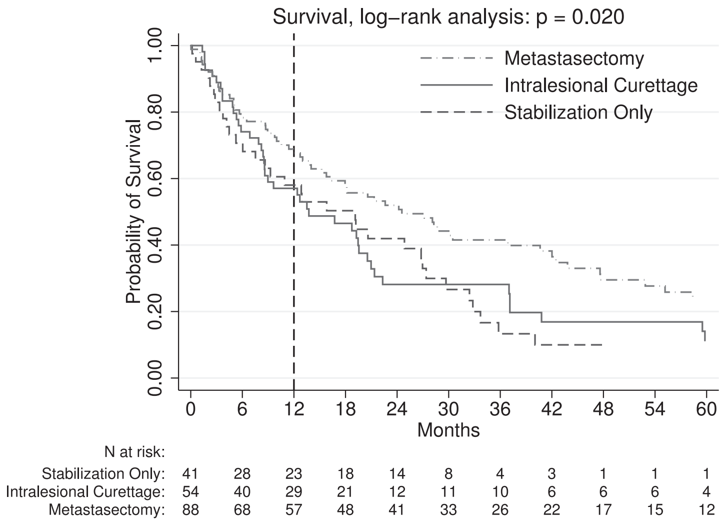

Figure 3: Survival probability in the metastasectomy group (dashed dot line), intralesional curettage group (solid line), and stabilization only group (dashed line) are shown.

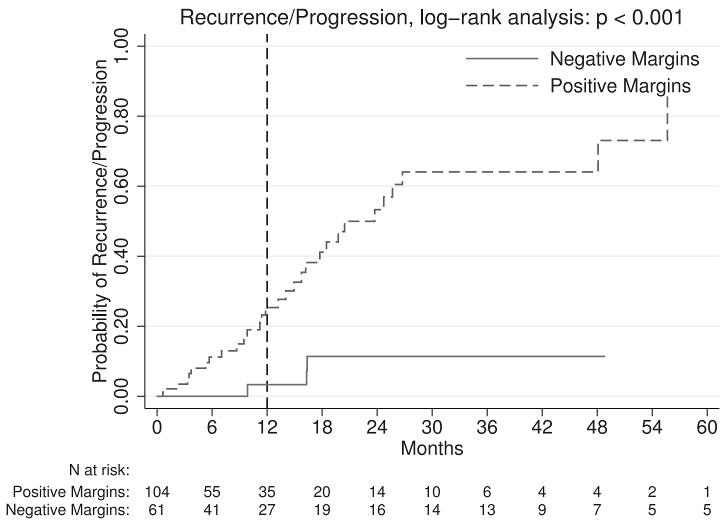

Figure 4: Local recurrence probability in the negative margins group (solid line) and positive margins group (dashed line) are shown.

The one-year reoperation probability was 0.19 (95% CI: 0.11 to 0.33) when a patient had negative margins and 0.11 (95% CI: 0.05 to 0.21) when a patient had positive margins. The five-year reoperation probability was 0.23 (95% CI: 0.15 to 0.44) when a patient had negative margins and 0.65 (95% CI: 0.36 to 0.92) when a patient had positive margins.

We found a better survival among patients who had negative margins ($p < 0.001$) (Figure 6). However, when we focused on patients with solitary bone metastases (24%, [44/183])

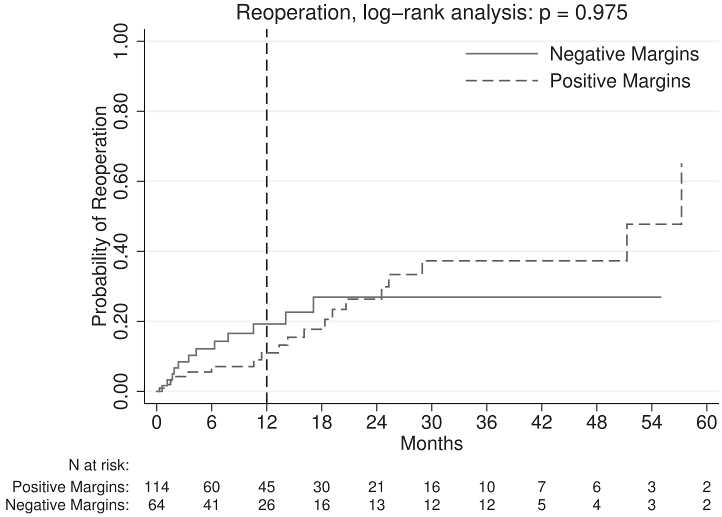

Figure 5: Reoperation probability in the negative margins group (solid line) and positive margins group (dashed line) are shown.

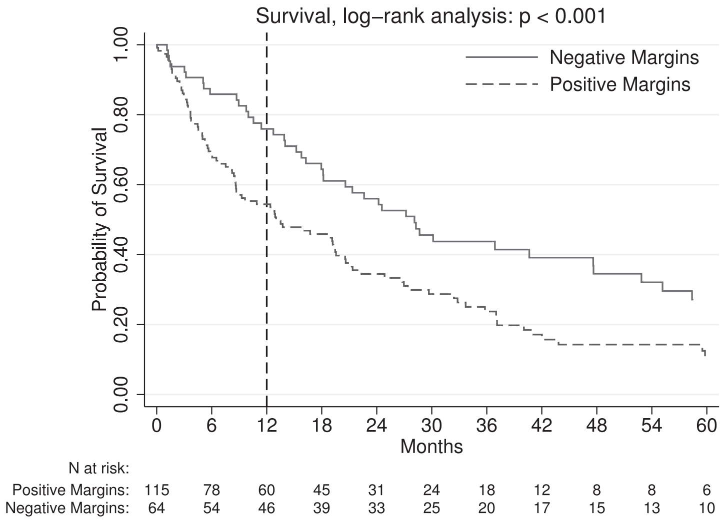

Figure 6: Survival probability in the negative margins group (solid line) and positive margins group (dashed line) are shown.

we found no difference, with the numbers evaluated, in survival between patients with negative margins and those with positive margins ($p = 0.35$). We did find a difference in survival based on margin status ($p = 0.015$) in patients with multiple metastases (76%, [139/183]); patients with negative margins had better survival than patients with positive margins.

DISCUSSION

The influence of surgical intervention on survival in patients with bone metastatic disease from renal cell carcinoma is previously described but studies are contradictory.[4,7,8,11] Conversely, the difference in local recurrence and reoperation rates after different surgical modalities are less commonly studied.[8,12] We therefore aimed to assess difference in these outcomes between patients who underwent metastasectomy, intralesional curettage, and surgical stabilization only for renal cell carcinoma bone metastases in a relatively large cohort of patients. We found a difference in local recurrence rate based on surgical strategy; recurrence rate was highest after stabilization only, followed by intralesional curettage, and metastasectomy. However, we found no difference in overall reoperation rates between strategies. Overall survival was better in patients who underwent metastasectomy and those who had negative surgical margins; however, this difference did not hold when focusing on patients with solitary bone metastases. Albeit, our sample size of patients with solitary metastasis might have been too small to detect a difference in this subanalysis.

A study by Evenski et al.[12] showed higher local recurrence rate after intralesional procedures (27%) as compared to wide resections (5%) in 86 patients with a renal cell metastasis of the appendicular skeleton. Another study by Les et al.[8] demonstrated a reoperation rate for tumor progression of 41% after internal fixation (with or without curettage and cement augmentation) as compared to 2.7% after marginal or wide resection (with or without reconstruction) in 78 patients with osseous renal cell metastasis. These previously reported differences are comparable to our findings; we found a 39% local recurrence rate in the stabilization only group, 22% in the intralesional curettage group, and 12% in the metastasectomy group. Residual tumor –after stabilization only and intralesional curettage– most likely explains the higher local recurrence (or progression) rate as compared to enbloc resection. This is supported by our comparison of recurrence rate based on margin status: the recurrence rate was 5% (3/64) in patients with negative margins, while it was 26% (30/115) in those with a positive margin. Four recurrences (20%, [4/20]) occurred in the enbloc metastasectomy group with positive margins.

Focusing on reoperations, we found no difference –with the numbers evaluated– in reoperation rates between the surgical strategies. The previous studies by Evenski et al.[12] and Les et al.[8] reported on reoperation rates for local recurrence, but did not report other reasons for reoperation. Our study demonstrated that reoperations in the metastasectomy group were mainly performed for deep infection and tumor recurrence, while recurrence was the main reason for reoperation in the intralesional curettage and stabilization only groups. Deep infections seem to occur early (Table 3), while local recurrence tends to occur late. This emphasizes the importance of incorporating life expectancy in surgical decision making. Metastasectomy –with negative margins in particular– reduces the chance of local recurrence and subsequent reoperation, but seems to come at the cost of a slightly higher early deep infection rate. In addition, the surgeon needs to consider the potential morbidity (e.g. other complications, blood loss, hospital stay, rehabilitation, disability) caused by large resections that aim to achieve negative margins and subsequently require complex reconstructions (e.g. pelvic resection followed by saddle prosthesis).

Our overall one-year survival probability of 62% is comparable with previous studies.[2,4] In line with previous investigations, we found better survival in patients who underwent metastasectomy as compared to those who underwent intralesional curettage or stabilization only.[8,18,19] However, this analysis is confounded by the difference in metastatic load between groups as demonstrated by our subanalysis in patients with solitary metastasis. To avoid this confounding effect, previous studies focused on survival in patients with solitary metastases only. Ratasvuori et al.[20] found a median survival of 50 months (95% CI: 16 to 84 months) in 21 patients who underwent enbloc resection as compared to a median survival of 15 months (95% CI: 8.8 to 21 months) in 34 patients who underwent intralesional surgery for solitary renal cell metastasis; however, confidence intervals overlapped indicating no statistical significance. Lin et al.[4] found no significant difference ($p = 0.52$) between a median survival of 45 months in 33 patients who underwent enbloc resection and a median survival of 22 months following curettage in 15 patients for solitary renal cell metastasis. Fuchs et al.[7] also found no difference in survival when comparing 13 patients with metastasectomy and 20 patients with intralesional curettage for solitary renal cell metastases. In line with these trends, we found a median survival of 43 months in the 30 patients who underwent metastasectomy, a median survival of 20 months in 12 patients who underwent intralesional curettage, and a median survival of 27 months in 2 patients who underwent stabilization only; however, this difference was also not significant. All studies suggest a trend towards better survival in the metastasectomy group as compared to intralesional treatment, but sample sizes are relatively small compromising the power of the statistical analyses.

Based on our findings, we feel that patients with a relatively good prognosis –life expectancy of more than one year– would benefit from enbloc resection with negative margins to improve local tumor control in the long term. In addition, metastasectomy –aiming to achieve negative margins– should be discussed with patients who have solitary or oligometastatic disease and have a reasonable prognosis as it might improve survival. Several models to estimate life expectancy in patients with bone metastatic disease have been developed; estimates from these models can be incorporated in surgical decision making.[21-23] However, a prognostication model that is specific for patients with bone metastases for renal cell carcinoma might be more accurate and useful. A future study that develops and externally validates such as model might as well incorporate a treatment algorithm based on life expectancy estimates and metastatic load.

Our study has limitations. First, the retrospective methodology jeopardizes the quality of collected data. We might have missed patients because of misspellings or simply missing information; however, we used common synonyms and misspellings and queried both pathology and operation reports to minimize this. In addition, we used the social security death index to establish date of death and inaccuracies in this database exist. However, the database is most accurate for older and oncology patients.[15] We see these as minor limitations as most likely, these occurred irrespective of surgical strategy and outcome or margin status and therefore, did not substantially influence our results. The retrospective design caused variation in followup. We tried to account for this using time-dependent analysis; however we were not able to track if patients went to a different institution for a local recurrence or reoperation. We see this as a minor limitation as we believe that this occurred irrespective of the surgical strategy and therefore did not compromise our comparison. Furthermore, our two-year loss to clinical followup rate was relatively low at 12%. In addition, there is heterogeneity as surgeries were performed by ten different orthopaedic oncologists over a 25-year period. Indications for the surgical techniques differed, could have varied between surgeons, and preferences might have changed over time. We see this as an important limitation of our study and therefore, we explored differences in baseline characteristics between the surgical strategies and ran subanalyses on survival to understand how this selection bias might have affected our outcome measures. Nevertheless, medical treatment has changed over time and the impact of medical treatment in survival cannot be taken into consideration in this study due to its retrospective nature. Furthermore, we feel that the effect of postoperative radiation had a limited or rather minimal effect on tumor recurrence and reoperation analysis. Postoperative radiation was more commonly given after intralesional curettage (33%), and stabilization only (59%), as compared to metastasectomy (8%). Nevertheless, recurrence rates remain higher in the first two groups. Lastly, our sample size could have been insufficient. We believe that the observed better survival after metastasectomy when compared to intralesional curettage and stabilization only might be confounded by the lower metastatic load (i.e. higher proportion of patients with solitary metastases) in the metastasectomy group. We therefore deployed subanalyses in patients with solitary metastasis, in which no difference in survival was demonstrated when comparing surgical strategies. However, post-hoc power analysis demonstrated that this subanalysis is underpowered due to its relatively small sample size (n = 44); the achieved power for this analysis was only 0.031 and we would have needed 45,997 patients to find a difference assuming a similar effect. A post-hoc power analysis for survival based on margin status in patients with solitary metastasis demonstrated that the achieved power was 0.21 and we would have needed 249 patients to demonstrate better survival among patients who had negative margins compared to positive margins. In the same line, the number of patients who underwent a reoperation (19%) was relatively small and could have resulted in insufficient power to detect differences among surgical strategies.

In conclusion, the risk of developing a local recurrence is higher among patients who undergo intralesional curettage or stabilization only as compared to patients who undergo metastasectomy. Enbloc resection with negative margins results in the lowest risk of local recurrence. The overall risk of reoperation does not differ between surgical strategies nor does it differ based on margin status; However, tumor recurrence is the main reason for reoperation after intralesional curettage and stabilization only, while early deep infections requiring reoperation occur more often after metastasectomy. Overall survival was better after metastasectomy and resection with negative margins, but these findings were confounded by the difference in metastatic load. A larger sample size, perhaps by combining the data from multiple institutions, is needed to determine the benefit of metastasectomy in patients with solitary or oligometastatic bone disease.

Our findings emphasize the importance of obtaining negative margins in patients with a relatively good life expectancy (i.e. in patients with a low oncologic burden), as a lower recurrence rate can be attained at a comparable risk for reoperation, with a potential impact on survival.

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Appendix 1: Implant type per anatomic area

			n = 183
Anatomic location	**Operation type**	**Implant type**	**n (%)**
Femur (n = 75)	IMN (n = 32)	Intramedullary nailing	32 (43)
	EPR (n = 31)	MTP Bipolar hemiarthroplasty	18 (24)
		MTP - Knee (Hinge)	6 (8)
		MTP With Cup	4 (5)
		Intercalary prosthesis	1 (1)
		Link Saddle Prosthesis	1 (1)
		Total Hip Arthroplasty	1 (1)
	ORIF (n = 10)	Plate screw fixation	10 (13)
	Resection (n = 2)	Girdlestone	1 (1)
		Curettage only	1 (1)
Humerus (n = 52)	IMN (n = 16)	Intramedullary nailing	16 (31)
	EPR (n = 19)	MTP - Shoulder hemiarthroplasty	12 (23)
		Hemiarthroplasty long-stem (head)	5 (10)
		Hemiarthroplasty (head)	1 (2)
		Total elbow	1 (2)
	ORIF (n = 16)	Plate screw fixation	16 (31)
	Resection (n = 1)	Curettage only	1 (2)
Acetabulum (n = 11)	EPR (n = 9)	Total hip arthroplasty	6 (55)
		MTP With Cup	2 (18)
		Link Saddle Prosthesis	1 (9)
	ORIF (n = 2)	Plate screw fixation	2 (18)
Pelvis (n = 11)	EPR (n = 1)	Link Saddle Prosthesis	1 (9)
	ORIF (n = 3)	Plate screw fixation	3 (27)
	Resection (n = 7)	Resection only	7 (64)
Tibia (n = 8)	IMN (n = 3)	Intramedullary nailing	3 (38)
	EPR (n = 2)	MTP - Knee (Hinge)	2 (25)
	ORIF (n = 2)	Plate screw fixation	2 (25)
	Resection (n = 1)	Curettage only	1 (13)
Femur and Acetabulum (n = 8)	EPR (n =8)	MTP - Hemiarthroplasty	5 (63)
		Total Hip Arthroplasty	2 (25)
		MTP With Cup	1 (13)
Scapula (n = 5)	Resection (n = 5)	Resection only	5 (100)
Ulna (n = 3)	IMN (n =1)	Intramedullary nailing	1 (33)
	ORIF (n = 2)	Plate screw fixation	2 (67)
Clavicle (n = 3)	Resection (n = 3)	Resection only	3 (100)
Calcaneus (n = 3)	ORIF (n = 1)	Plate screw fixation	1 (33)
	Resection (n = 2)	Curettage only	2 (67)

Appendix 1: Implant type per anatomic area (*continued*)

			n = 183
Anatomic location	**Operation type**	**Implant type**	**n (%)**
Radius (n = 1)	ORIF (n = 1)	Plate screw fixation	1 (100)
Metatarsal (n = 1)	ORIF (n = 1)	Plate screw fixation	1 (100)
Metacarpal (n = 1)	Resection (n = 1)	Curettage only	1 (100)
Ulna and Metacarpal (n = 1)	ORIF (n = 1)	Plate screw fixation, both	1 (100)

IMN = intramedullary nailing, EPR = endoprosthetic reconstruction, ORIF = open reduction and internal fixation, MTP = modular tumor prosthesis

Appendix 2: Modified Charlson Comorbidity Index Algorithm Based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Codes

Comorbidity	Weight*	Codes
AIDS/HIV	4	042
Any malignancy, including leukemia and lymphoma*	2	150.0-159.0, 162-173.59, 173.70-175.9, 180.0-183.9, 185-186.9, 188.0-188.6, 188.8-189.4, 189.9, 191.0-192.3, 192.9-194.4, 200.2-202.38, 202.70-202.81, 203.0-204.22, 204.90-208.22, 208.90-209.36, 209.70, 209.72-209.79, 230.2-230.6, 230.8, 231.2, 231.9, 232.5-232.7, 233.0, 233.1, 233.31, 233.32, 233.4, 233.7, 235.2-235.4, 235.7, 235.8, 236.2, 236.4, 236.5, 236.7-236.91, 237.1-237.4, 237.6, 238.0-238.3, 238.79, 239.0-239.4, 239.6, 239.7, 239.89, 239.9
Chronic pulmonary disease	1	416.8, 416.9, 490-491.0, 491.2-495.2, 495.4-505, 506.4, 508.1, 508.8
Congestive heart failure	2	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428-428.43
Dementia	2	290, 290.0, 290.3, 290.8-290.43, 294.1, 294.11-294.21, 331.2
Diabetes with chronic complications	1	249.40-249.91, 250.40-250.90
Hemiplegia or paraplegia	2	342.00-342.92, 344.00-344.5, 344.89-344.9
Metastatic solid tumor*	6	197.0-198.7, 198.81-190.9, 192.0-196.9, 199.0
Mild liver disease*	2	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 570.1, 573.3, 573.4, 573.8, 753.9, V42.7
Moderate or severe liver disease*	4	456.0-456.2, 572.2-572.8
Renal disease	1	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582-583.7, 585-586, 588.0, V42.0, V45.1, V56-V56.8
Rheumatologic disease	1	466.5, 710.0-710.4, 714.0-714.2, 714.8, 725

*The following comorbidities were mutually exclusive: mild liver disease and moderate or severe liver disease, and any malignancy and metastatic solid tumor. For example, a patient with a metastatic solid tumor received 6 points total (not 6 points for metastatic solid tumor and 2 points for any malignancy).