Who is dying after nephrectomy for cancer? Study of risk factors and causes of death after analyzing morbidity and mortality reviews. (UroCCR-33 study)

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INTRODUCTION

Renal cell carcinoma (RCC) represents 3% of all cancers (1). The incidence of RCC has increased worldwide and in Europe (2) due to the use of abdominal imaging (3). Surgical treatment such as radical and partial nephrectomy is recommended for T1-4 tumours. The improvement of surgical techniques and peri-operative care has diminished peri-operative morbidity (4). However, nephrectomy remains at risk: studies suggest that the thirty-day mortality (TDM) after nephrectomy ranges between 0.6% and 3.6% (5-7). It has been suggested that the TDM rate is related to age, disease stage and type of surgery (7).

To our knowledge, there is no data in the literature reporting outcomes and measurements of morbidity and mortality reviews after nephrectomy. Our objective was to determine the TDM rate after nephrectomy for cancer in a large multicentric database as well as identifying causes of and risk factors of death.

METHODS

After approval from each institutional review board, we performed a retrospective study on a prospective database involving seven centers (Toulouse, Bordeaux, Poitiers, Rennes, Henri Mondor, Reims and Angers University Hospitals) part of the French network for research on kidney cancer UroCCR (ClinicalTrials.gov: NCT03293563).

The data of patients who had been treated by surgery for a renal tumor between 2014 and 2017 were prospectively collected in the national registered institutional review board approved multicenter database UroCCR (CNIL agreement DR-2013-206). Upper-tract transitional cell carcinomas and non-cortical renal tumours (melanomas, sarcomas, and lymphomas) were not included. Pre and post-operative parameters such as age, sex, local symptoms (hematuria, lower back pain, abdominal mass) and general (fever, general status, paraneoplastic syndroms), cTNM stage, type of procedure (open, laparoscopic, robot-assisted surgery), type of surgery (partial, radical nephrectomy), time to death and death cause were recorded.

We identified all patients who died after nephrectomy for cancer during the first thirty days and we analyzed causes of death. We used TDM that is often used to describe mortality after surgical interventions (9-10).

For every deceased patient, we looked at medical and MMR reports in order to find out about the analysis of the case and clinical conclusions.

The SPSS®, version 20.0 software package was used for all statistical analyses. Independent-sample t-tests and chi-square tests were used for comparisons of quantitative and qualitative variables, respectively. Univariate and multivariate regression models were used to assess the influence of different variables on post-operative death.

RESULTS

Causes of TDM

The main cause of postoperative death was pulmonary (n=15, 43%): 11 patients died of pneumonia or inhalation (29%) and 5 patients of pulmonary embolism (14%). Among those five patients, three had a caval thrombus (9%). The second leading cause was postoperative digestive sepsis in 7 (20%) patients. Hemorrhage was the third cause with 4 (11%) patients. Three patients died from their cancer (9%). Liver failure and heart failure were found in 2 patients (6%). Neurological and Multiple organ dysfunction syndrom were found in one (3%) patient each. Causes of TDM causes are reported in table 1.

Thirty-day mortality rate

From 2014 to 2017, 2578 patients underwent nephrectomy and 35 deaths occurred during the initial thirty days. The TDM rate was 1.4%. The median time to death was 10.5 days (range: 0-30).

Characteristics of patients who died in the thirty days after nephrectomy

Among the 35 deceased patients, median age was 71 years (extremes: 40-86), 27 (77%) were male and 8 (23%) were female. Local and systemic symptoms at diagnosis were present in respectively 12 (34%) and 8 (23%) patients. Radical and partial nephrectomy were performed in 25 (71%) and 10 (29%) patients, respectively. Open, laparoscopic and robotic surgeries were performed in 20 (57%), 13 (37%) and 2 (6%) patients, respectively. There were 9 (27%) pT1, 5 (15%) pT2, 17 (49%) pT3 and 2 (6%) pT4 tumours. Seven patients had lymph node involvement (20%) and eight had a metastatic disease (23%). ASA scores, ECOG scores and others patients' characteristics were reported in table 2.

Risk factors of TDM

In univariate analysis symptoms at diagnosis ($p=0.006$, $OR=2.56$ IC(1.3-5.03)), c stage

superior to cT1 ($p<0.0001$, OR=6.13 IC(2.8-13.2)), cT stage superior to cT2 ($p<0.0001$, OR=8.8 IC(4.39-17.8)), nodal invasion ($p<0.0001$, OR=4.6 IC(1.9 -10.7)), distant metastasis ($p=0.001$, OR=4.01 IC(1.7-8.9)), open surgery ($p<0.0001$, OR=0.272 IC(0.13-0.54)) and radical nephrectomy ($p=0.007$, OR=2.737 IC(1.3-5.7)) were significantly associated to TDM. In the multivariable model only cT stage > T2 ($p=0.015$, OR=3.55 IC(1.27-10.01)) was an independent predictor of TDM (table 3).

DISCUSSION

In our study, we found a thirty-day mortality rate of 1.4% and identified several risk factors of TDM including symptoms at diagnosis, cTNM and operative techniques. Symptomatic patients with a large advanced tumour are the most at risk especially after radical nephrectomy.

In the available literature, the overall TDM rate is around 0.55% (PN 0.10%; RN 0.52%) (15-16). Cloutier and al. (7) reported similar findings with a TDM rate of 0.9%. Beisland and al. (8) reported similar risk factors of TDM but also found hospital volume to be an independent parameter of TDM (11-14). The mortality rate of nephrectomy seems to decrease over time: it went down from 3.1% between 1978 to 1997 (8) and 2.8% between 1970 and 2000 (17). This decrease in mortality probably results from a better patient selection and from the improvement of minimal-invasive surgical techniques and peri-operative care.

In our cohort, pulmonary affections, namely pneumonia and embolism, were the leading cause of TDM after nephrectomy. The second cause was digestive sepsis including peritonitis, intestinal perforation or necrosis. Looking at our results, some deaths could have probably been avoided: 3 of our patients died in the post-operative period because of a poor general status related to advanced cancer. It is highly probable that these three metastatic patients were not carefully selected and should not have been operated. These deaths underline the limit of cytoreductive nephrectomy that should be decided on a case by case basis according to prognosis and life expectancy (18).

We analyzed every medical report and found only two reports of MMR. The first patient died from bilateral pulmonary embolism during surgery. He had a level 3 caval thrombus which probably spread out quickly after the cavotomy. The multidisciplinary meeting lead surgeons to better evaluate preoperative extension of the thrombus in order to better predict peri-operative needs (collaboration of cardiothoracic surgeons, resort to this extracorporeal circulation). The second patient died from postoperative hemorrhage on day 2. He was a

frail patient of 79 years old with many cardiac affections including a mechanic mitral valve. He was taking antiplatelet, anticoagulant and antiarytmics drugs. The MMR identified a failure in the post-operative management especially in the management of anticoagulation. The multidisciplinary meeting lead surgeons to a general evaluation in the hospital of postoperative use of unfractionated heparin, to realize a precise heparin protocol and to a systematic medical oversight during the two or three first postoperative days in a surgical care intensive unit for this type of patient.

We were very surprised to find only two MMR reports for the 35 patients. The first reason for our surprise was that MMRs are suggested by all surgical guidelines. The main aim is to improve patient' care and safety with a multidisciplinary reviewing of all death circumstances (19). MMR can be seen as a “post-operative black box” similar to a flight recorder with the aim of facilitating the investigation of medical accidents and incidents. MMRs often take place in surgical environments and provides practical advice that participates to medical education (20). Antonacci et al. (21) suggested that in surgical departments, MMRs can decrease the mortality by 40%.

We believe our results are of interest: data was extracted from a multicentric and prospectively maintained database in a modern era. However there are several limits. The TDM criteria is the most used in studies but it is not perfect and it may be questionable to think that mortality within 30 days is always related to surgery. Also, TDM does not evaluate the subjective dimension of postoperative quality of life of patients after nephrectomy. Also, this prospective study is based on declarative data submitted by surgeons who participate in the UroCCR project. There were no obligation to include all nephrectomy and for the included patients, some files were deficient with a lack of descriptive data. Finally, this multicentric study may pose a problem of external validity because it relies on a French population that is not necessarily representative of other populations.

CONCLUSION

Our results show that mortality after nephrectomy for cancer is minimal and mostly driven by comorbidities and tumour stage. Pulmonary affections are the leading causes of death in our French cohort.

Authorship form

Study concept and design: Fontenil, Bigot, Bensalah, Bernhard.

Acquisition of data: Fontenil, Latxague.

Analysis and interpretation of data : Fontenil, Bigot.

Drafting of the manuscript: Fontenil, Bigot, Bensalah.

Critical revision of the manuscript for important intellectual content: Bigot, Bensalah, Bernhard.

Statistical analysis: Bigot.

Obtaining funding: None.

Administrative, technical, or material support: Latxague, Bernhard, Bigot.

Supervision: Fontenil, Bigot, Bensalah.

Other (specify): None.

Author contributions: Alexis FONTENIL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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TABLES

Table 1. Causes of post-operative deaths.

Table 2. Dead patient demographics and tumor characteristics.

Table 3. Univariable and multivariate analysis of risk factors of postoperative death after nephrectomy.

Table 1. Causes of death.

Causes	n=35(%)
Pulmonary	15(43)
Pneumonia or Inhalation	10(29)
Pulmonary embolism	5(14)
Digestive sepsis	7(20)
Hemorrhage	4(11)
Related to cancer	3(9)
Liver failure	2(6)
Heart failure	2(6)
Neurological	1(3)
Multiple organ dysfunction syndrome	1(3)

Table 2. Dead patient and tumor characteristics.

Characteristics	n=35
Sex, n (%)	
Male	27 (77)
Age, year	64 (40-86)
BMI, kg/m2	27
Symptoms at diagnosis, n (%)	
Asymptomatic	15 (43)
Local symptoms	12 (34)
Systemic symptoms	8 (23)
ASA score, n (%)	
ASA 2	17(48)
ASA 3	15(44)
ASA 4	3(8)
ECOG status, n (%)	
ECOG 0	12 (34)
ECOG $\geq$ 1	23 (66)
Medical history, n (%)	34 (97)
Hypertension	19 (54)
Diabetes	10 (29)
Dyslipidemia	10 (29)
Smoking	7 (20)
Antiplatelet or anticoagulant drugs	11 (31)
Deep vein thrombosis or pulmonary embolism	4 (11)
Renal failure	4 (11)
Treatment type, n (%)	
Radical nephrectomy	25(71)
Partial nephrectomy	10(29)
Open surgery	20(57)
Laparoscopic	13(37)
Robotic	2(6)
Histological subtype, n (%)	
Clear cell RCC	28(80)
Papillary RCC type 1	4(11)
Papillary RCC type 2	2(6)
Angiomyolipoma	1(3)
Clinical tumor stage, n (%)	
T1	9(27)
T2	5(15)
T3	17(49)
T4	2(6)
N1	7(20)
M1	8(23)

Table 3: Univariable and multivariate analysis of risk factors of postoperative death after nephrectomy.

Variable	Univariate analysis			Multivariate analysis	
	Total	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Sex					
Male	1647	1			
Female	896	0.54 (0.24 - 1.2)	0.115	0.51 (0.21-1.2)	0.131
Age, years	NA	1.027 (0.99-1.05)	0.058	1.024 (0.99-1.05)	0.129
Symptoms at diagnosis					
no	1689	1			
yes	890	2.56 (1.3-5.03)	0.006	1.09 (0.48-2.46)	0.822
Initial cT stage					
T1	1515	1			
>T1	679	6.13 (2.8-13.2)	<0.0001	1.55 (0.45-5.37)	0.48
> T2	306	8.8 (4.39-17.8)	<0.0001	3.55 (1.27-10.1)	0.015
Initial cN stage					
0 or X	2441	1			
1-2	138	4.6 (1.9 -10.7)	<0.0001	1.26 (0.48-2.46)	0.63
Initial cM stage					
0 or X	2396	1			
1	183	4.01 (1.7-8.9)	0.001	1.3 (0.52-3.25)	0.57
Operative technique					
open surgery	807	1			
laparoscopic or robotic surgery	1718	0.272 (0.13-0.54)	<0.0001	0.65 (0.29-1.47)	0.3
Operative type					
partial nephrectomy	1326	1			
radical nephrectomy	1227	2.737 (1.3-5.7)	0.007	1.35 (0.48-3.82)	0.56