Safety and feasibility of laparoscopic nephrectomy for big tumors (10 cm): a retrospective multicentric study

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Safety and feasibility of laparoscopic nephrectomy for big tumors (≥10 cm): a retrospective multicentric study.

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Clinical Practice Points:

* What is already known about this subject?

Few series with small samples have been published. This study remains the biggest in the literature on the subject in collaboration with several centres through Europe and USA.

* What are the new findings?

Complication rates and positive surgical margins are similar to open surgery.

* How might it impact on clinical practice in the foreseeable future?

Open surgery is still the gold standard for tumors >10 cm. This study demonstrates the safety of laparoscopy in such indication, with comparable rates of complications and positive margins.

Abstract

Objective: Evaluate the feasibility of laparoscopic nephrectomy (LN) for big tumors.

Material & Methods: Data from 116 patients were retrospectively collected from 16 tertiary centres. Clinical and operative parameters, tumor characteristics, per and post operative parameters and renal function before and after surgery were analyzed.

Results: Mean age and BMI were 61 y.o and 27.8 kg/m², respectively. Males represented 63.8% and 54.4% presented symptoms at diagnosis. Median tumor size was 11 cm and 75% of the cases were performed by expert surgeons. Median operative time and blood loss were 180 min and 200ml respectively. Conversion to open surgery was necessary in 20.7%. Intra operative complications related to massive haemorrhage occurred in 16.4%, resulting in open conversion in 62.5%. Major postoperative complications occurred in only 10 patients (8.6%). In univariate analysis, intra operative complications, age and blood loss were predictive factors of conversion to open surgery. Positive surgical margins occurred in 6 patients (5.2%). None of them presented a local recurrence. Predictive factors of recurrence or progression were lymph node invasion, metastases and Furhman grade.

Conclusion:

LN for tumors>10 cm can be performed safely. Complication rate and positive surgical margins are similar to open surgery. In experienced hands, the benefit of a mini invasive surgery remains evident.

Microabstract

116 patients who had a laparoscopic nephrectomy (LN) for big tumors were included. Conversion to open surgery was necessary in 20.7%.Haemorrhage occurred in 16.4%, resulting in open conversion in 62.5%. Intra operative complications, age and blood loss were predictive factors of conversion to open surgery. LN for tumors>10 cm can be performed safely with comparable results to open surgery.

Introduction

The management of renal tumors has greatly evolved over the last decades. Renal lesions are discovered at an earlier stage and these small renal masses are mostly treated by partial nephrectomy[1].

However, urologists are still confronted to large tumors that require a radical nephrectomy. Because of decreased morbidity, laparoscopic radical nephrectomy (LRN) has become the standard treatment of T1 and T2a tumors that are not amenable to partial nephrectomy. Many studies have confirmed that oncological outcomes were similar to that of open surgery[2].

With growing experience of surgeons worldwide, the laparoscopic approach has progressively been extended to voluminous kidneys[3] (such as the ones seen in polycystic kidney disease), and despite technical difficulties, some teams routinely consider LRN for big renal tumors[4-7]. However, there have been concerns regarding the safety of laparoscopy for the excision of bulky renal tumors and there is limited published data on oncological outcomes of LN for big renal tumors.

Our objective was to evaluate the outcomes of LRN for large renal tumors (defined as > 10cm) in a contemporary multicentric series.

Material & Methods

Study design

This was a retrospective study that included 116 patients who underwent pure LRN for a large tumor (defined as a diameter > 10 cm on pathological exam). Patients included underwent surgery between 2004 and 2013. After institutional approval, data were extracted from kidney cancer databases from 16 tertiary urological centres with common practice of LRN in France, the Netherlands, Turkey, Czech Republic and the United States. There was no robotic or hand-assist procedures. Patients with caval thrombus were excluded. Lymphadenectomy was not systematically performed and was left at the surgeon's discretion.

Some patients had metastatic disease and received adjuvant interferon, interleukin 2-based immunotherapy or more recently antiangiogenics treatments. Post-operative follow-up was specific to each institution.

Data collection

Clinical parameters included age, gender, body mass index (BMI), Charlson comorbidity index, history of hypertension or diabetes mellitus, Eastern Cooperative Oncology Group (ECOG) performance status (PS), ASA score, symptom score (S classification), need for post operative haemodialysis. Data regarding kidney function included pre and post operative glomerular filtration rate (GFR) estimated by the abbreviated Modification of Diet and Renal Disease (MDRD) equation[8].

Pathological features included tumor size, histological subtype, TNM stage (2009 TNM classification [9]), and Fuhrman grade. Histological subtypes were stratified according to the World Health Organization classification [10].

The following peri-operative parameters were analyzed: type of surgery (robotic or laparoscopic), operative time, blood loss, transfusion rate, location of the tumor (upper, mid or lower pole), intra and post-operative complications (graded according to Clavien's classification), length of hospital stay, and surgeon's experience (a surgeon was considered experienced if he had performed more than 20 LRN as defined in several studies[5-7]).

Intra operative complications included those that required immediate treatment, such as vascular or organ injury and were not considered in the post operative Clavien's classification. Conversion to open surgery was not considered as a complication.

At last follow up, patients were considered as living (with or without disease) or deceased (from renal cancer or from any other cause).

Statistical analyses

Continuous variables are presented as mean ± standard deviations or median ± inter-quartile range (IQR). Categorical variables are presented as counts and percentages. Association between binary outcomes (i.e., surgical conversion, post-operative complications and cancer recurrence/progression) and selected covariates was assessed using either Fisher exact test (for binary covariates) or ridit score (for ordinal covariates) or Wilcoxon test (for continuous covariates). Odds ratio and 95% Wald confidence limits were used as measure of association. Covariates statistically associated in univariate analyses were considered for multivariate logistic regression modeling. All analyses used procedures from SAS 9.3 (SAS Institute, Cary, N.C., USA).

Results

Mean age was 61 years old and most of the patients were males (64%). Mean BMI was 27.8 kg/m². The majority of the population had few co morbidities (81.6% of ASA score 1-2 and median Charlson comorbidity index score of 2). 53.4% of the patients had local or general symptoms, and 37.2% had an altered performance status (table 1).

Operative parameters

Most of the procedures (75%) were performed by expert surgeons. Median tumor size was 11 cm. Median operative time was 180 min, and median blood loss was 200 ml. Intra operative complications occurred in 16.3% of the cases and were all related to haemorrhage. A conversion to open surgery was necessary in 20.7% of the cases, mostly because of intra operative bleeding or a difficult dissection related to tumor volume. In case of intra operative complication, a conversion to open surgery was needed in 62.5% of the cases. One third of the patients had post operative complications, but the majority was low grade (10 patients had a high grade complication) (Table 1). 6% of the patients had to be reoperated. Reoperation was mainly related to post-operative hemorrhage. One patient presented bleeding from the adrenal, another had to have a splenectomy, two had bleeding from the abdominal wall (epigastric vessel injury), and one had a wound abscess that needed surgical drainage. Finally, only one patient had an abdominal repair at distance due to evisceration There was no death secondary to surgery.

Pathological examination and clinical evolution

Pathological analysis showed that most of the tumors were of high stage and grade, and clear cell carcinoma was the most frequent histological subtype (table 1). Seven patients had a positive margin and one had metastatic progression at 6 months. Local recurrence was observed in ten patients (8.7%). Fifteen patients (12.9%) had metastatic progression and 12.1% died from their cancer.

Predictive factors of surgical conversion and complications

In univariate analysis, age, blood loss and intra operative complications were associated with a significant risk of conversion. Less experienced surgeons had more open conversions although not significant (p= 0.059) (table 2). In multivariate analysis, the only predictive factor of conversion was the occurrence of an intra operative complication (OR 26.3; p= 0.001).

Factors associated with post-operative complications were the occurrence of an intra operative complication, operative time and surgeon's expertise (table 3). In multivariate analysis surgeon's experience tended to be associated with the occurrence of a post-operative complication (p= 0.06).

Predictive factors of recurrence/progression and progression free-survival

Since there was a limited number of local recurrence and/or metastatic progression, we considered those two events similarly as cancer recurrence. Variables associated with cancer recurrence were: lymph node invasion, presence of metastases at diagnosis, and Fuhrman grade. Operative parameters such as blood loss, operative time and conversion to open surgery or complications had no impact on progression free survival (table 4). Similarly a positive surgical margin did not increase the risk of cancer progression (p= 0.97).

Progression-free survival analysis was conducted in 112 patients with malignant tumors (two patients had benign tumors on final histology, and in two others, pathology was missing). Twenty one patients experienced a pre-specified qualifying event: 6 recurrences, 12 progression and 3 cancer deaths. Median time to event occurrence was 6 months (min, max [IQR]: 2, 29 [4-12]). Kaplan-Meier survival estimates for progression-free survival are displayed in figure 1.

Discussion

LRN has become the standard of care for the treatment of localized kidney tumors not amenable to partial nephrectomy. It can be considered to treat larger tumors, but little is known about the outcomes of LRN for big tumors.

We report the results of a large multicentric series that shows that LRN for big renal tumors is feasible and safe: there was no death related to surgery and most of the complications that occurred were of low grade. However, it is technically challenging with an open conversion rate of 20%. Removing such large tumours requires an extended laparoscopic experience: working space is limited because of the volume of the kidney which makes the pedicle dissection more difficult. Significant neo-vascularisation is frequently encountered around the kidney which increases the risk of bleeding and conversion. However our median blood loss was 200 ml which is comparable to open series[11].

There is limited data in the literature concerning LRN for very large tumors. Several authors reported their experience of LRN for tumors >7 cm but median tumor size in those series was always < 10 cm with a limited number of patients with bulky tumors[4, 5, 12, 13].

When compared to open series[12 13], we had similar complications rate and a shorter length of stay. Therefore, it seems that the benefits of laparoscopy observed for smaller renal tumors are also present for large renal masses[4, 12, 13]. In a multicentric study comparing LRN with open surgery for tumors > 7cm, Jeon reported significantly less blood loss in the laparoscopic group (439 vs. 604 ml, p= 0.006), and comparable intra operative complication rates (10.2% vs. 14.4%, p= 0.34)[12]. In another study comparing LRN for tumors between 7 and 10 cm and for tumors > 10 cm, there was no difference in terms of peri-operative morbidity [5]. These results and ours show that provided that a surgeon has the expertise, laparoscopy can be considered for large tumors without any fear of increasing the risk of post-operative complications.

An important finding of our study is that LRN oncological outcomes are similar to that of open surgery. There have been concerns regarding the safety of laparoscopy, particularly for the removal of bulky tumors, with descriptions of port site recurrences or hypothetical fears of peritoneal dissemination related to the

pneumoperitoneum. However, with growing laparoscopic experience worldwide, many studies have put forward the safety of laparoscopy[5-7, 12, 13] even in the case of cytoreductive surgery[14]. Our study supports those findings in the subset of large renal tumors. Even in patients with positive margins, where one can hypothesize that there were tumoral effraction during surgery, we did not observe any increased recurrence rate. Only 8.7% of our patients had a local recurrence which is comparable to the 8.3-9.3% rates reported in open series for pT3 tumors[15, 16]. Such findings had already been reported for tumours > 7 cm [12]. Progression mostly occurred in patients with high stage and high grade disease.

Interestingly, most of the procedures were performed after 2008 which reflects the changing evolution of surgical practices. We don't have any data regarding the age of the surgeons who did the surgery but with the turnover of urologic surgeons' who were trained in the era of laparoscopy, it is highly probable that laparoscopic procedures will become more and more frequent even for challenging cases.

This study has several limits. First, this is a retrospective and multicentric study with inherent biases related to data recollection. The choice of laparoscopy was specific to each institution and we don't have any insight regarding selection criteria. Second, we don't have any open control group for direct outcome comparison. Finally there is some heterogeneity regarding the contribution of the centers involved in the study with 44% of the patients brought by three institutions. So there might be some variability regarding surgeon's expertise. Finally, follow-up is too short to optimally appreciate oncological safety.

Conclusion

Large renal tumours can safely be removed by laparoscopy, provided adequate surgical expertise. Conversion rate is high but complication rates are similar to that of open surgery. Additional follow-up is needed to ensure oncological outcomes are favourable.

The authors declare no conflict of interest.

Author's contribution:

- Grégory Verhoest and Karim Bensalah: study design, manuscript redaction
- Emmanuel Oger: statistical analysis
- Jean-Philippe Couapel, Nathalie Rioux-Leclercq, Géraldine Pignot, Jean-Jacques Patard, Axel Bex, Paul Panayotopoulos, Pierre Bigot, Viktor Eret, Milan Hora, Burak Turna, Maxime Lefevre, Jérôme Rigaud, Xavier Tillou, Arnaud Doerfler, Evanguelos Xylinas, Yanish Soorojebally, Morgan Rouprêt, Samuel Lagabrielle, Jean-Christophe Bernhard, Jean-Alexandre Long, Julien Berger, Emmanuel Ravier, Philippe Paparel, Laurent Salomon, Alejandro R Rodriguez: Data collection

Ethical standard statements:

Data were extracted from kidney cancer databases from 16 tertiary urological centres approved at each institution.

Bibliography

1. Patard JJ, Tazi H, Bensalah K, et al. The changing evolution of renal tumours: a single center experience over a two-decade period. Eur Urol. 2004; **45**(4): 490-3; discussion 3-4.
2. Ljungberg B, Hanbury DC, Kuczyk MA, et al. Renal cell carcinoma guideline. Eur Urol. 2007; **51**(6): 1502-10.
3. Verhoest G, Delreux A, Mathieu R, et al. Transperitoneal laparoscopic nephrectomy for autosomal dominant polycystic kidney disease. JSLS. **16**(3): 437-42.
4. Dillenburg W, Poulakis V, Skriapas K, et al. Retroperitoneoscopic versus open surgical radical nephrectomy for large renal cell carcinoma in clinical stage cT2 or cT3a: quality of life, pain and reconvalescence. Eur Urol. 2006; **49**(2): 314-22; discussion 22-3.
5. Pierorazio PM, Hyams ES, Lin BM, Mullins JK, Allaf ME. Laparoscopic radical nephrectomy for large renal masses: critical assessment of perioperative and oncologic outcomes of stage T2a and T2b tumors. Urology. 2012; **79**(3): 570-5.
6. Berger AD, Kanofsky JA, O'Malley RL, et al. Transperitoneal laparoscopic radical nephrectomy for large (more than 7 cm) renal masses. Urology. 2008; **71**(3): 421-4.
7. Luciani LG, Porpiglia F, Cai T, et al. Operative safety and oncologic outcome of laparoscopic radical nephrectomy for renal cell carcinoma >7 cm: a multicenter study of 222 patients. Urology. 2013; **81**(6): 1239-44.
8. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; **130**(6): 461-70.
9. Sobin LH, Wittekind C. TNM. Classification of malignant tumors. Sixth Edition. UICC International Union Against Cancer, Ed Willey-Liss. 2003: 193-5.
10. Lopez-Beltran A, Scarpelli M, Montironi R, Kirkali Z. 2004 WHO classification of the renal tumors of the adults. Eur Urol. 2006; **49**(5): 798-805.
11. Dave DS, Lam JS, Leppert JT, Belldegrun AS. Open surgical management of renal cell carcinoma in the era of minimally invasive kidney surgery. BJU Int. 2005; **96**(9): 1268-74.
12. Jeon SH, Kwon TG, Rha KH, et al. Comparison of laparoscopic versus open radical nephrectomy for large renal tumors: a retrospective analysis of multi-center results. BJU Int. 2011; **107**(5): 817-21.
13. Hemal AK, Kumar A, Kumar R, Wadhwa P, Seth A, Gupta NP. Laparoscopic versus open radical nephrectomy for large renal tumors: a long-term prospective comparison. J Urol. 2007; **177**(3): 862-6.
14. Matin SF, Madsen LT, Wood CG. Laparoscopic cytoreductive nephrectomy: the M. D. Anderson Cancer Center experience. Urology. 2006; **68**(3): 528-32.
15. Levy DA, Slaton JW, Swanson DA, Dinney CP. Stage specific guidelines for surveillance after radical nephrectomy for local renal cell carcinoma. J Urol. 1998; **159**(4): 1163-7.
16. Ljungberg B, Alamdari FI, Rasmuson T, Roos G. Follow-up guidelines for nonmetastatic renal cell carcinoma based on the occurrence of metastases after radical nephrectomy. BJU Int. 1999; **84**(4): 405-11.

Variables	Results
Mean age (years), mean ± SD	61 ± 13
Sex ratio: men, n (%)	74 (63.8)
HTA, n (%)	63 (54.3)
Diabetis mellitus, n (%)	18 (16.1)
ASA score, n (%) 1 2 3	25 (21.9) 68 (59.6) 21 (18.4)
Charlson comorbidity index score (n= 95), median [range]	2 [0-11]
Symptom, n (%) asymptomatic local symptoms general symptoms	54 (46.6) 45 (38.8) 17 (14.6)
BMI (kg/m²), mean ± SD	27.8 ± 5.8
ECOG = 0, n (%)	64 (62.7)
Expert surgeon (>20 LN), n (%)	75%
Operative time (min), median [IQR]	180 [130 – 211]
Blood loss (ml), median [IQR]	200 [100-500]
Tumor size (cm), median [IQR]	11 [10.2-17]
Hospital stay (day), median [IQR]	6 [4-7,5]
Follow-up (month), median [IQR]	15 [7- 34]
Conversion to open surgery: n (%) - bleeding - tumor volume/adhesions	24 (20.7) 13 (54.2) 11 (45.8)
Intra operative complications, n (%)	19 (16.4)
Medical complications, n (%)	16 (13.8)
Surgical complications, n (%)	16 (13.8)
Blood transfusion, n (%)	15 (12.9)
Major complications: Clavien ≥ 3, n (%)	10 (8.6)
Postoperative renal function: n (%) Down staged Stable Up staged	 47 (48.4) 36 (37.1) 14 (14.4)
pT stage: pT2b pT3a pT4	44 (39.6) 65 (58.6) 2 (1.8)
N0, n (%)	102 (91.9)
M1, n (%)	17 (15.3)
Fuhrman grade 3-4 (n=103)	73 (70.9)
Histologic subtypes: Clear cell Papillary Chromophobe Undetermined Benign tumors	77 (66.4) 21 (18.1) 10 (8.6) 6 (5.2) 2 (1.7)

Positive margins, n (%)	6 (5.2)
Local recurrence, n (%)	10 (8.7)
Progression, n (%)	15 (12.9)
Death from cancer, n (%)	14 (12.1)
Death, n (%)	17 (14.6)

Table 1: Epidemiological, operative characteristics, pathological and oncological parameters of the patients who had a LN for tumors >10 cm

Univariate	Variables	OR	95% CL	*p*
	Sex	1.34	0.53 - 3.35	0.63
	Age (per 10 years)	1.51	1.03 - 2.22	0.03
	ASA score 2 vs. 1 3 vs. 1	4.14 2.71	0.89 - 19.3 0.44 - 16.5	0.29
	Charlson comorbidity index 2 vs. 0-1 ≥ 3 vs. 0-1	0.48 0.98	0.10 - 2.64 0.23 - 5.08	0.31
	ECOG 1 vs. 0 2 vs. 0	0.69 0.60	0.24 - 1.98 0.06 - 5.53	0.85
	BMI (per 5 kg/m²)	0.97	0.64 - 1.42	0.98
	Surgical expertise	0.76	0.28 - 2.08	0.059
	Intra operative complications	36.6	10.0 - 134	< 0.0001
	Blood loss (per 200 mL)	1.76	1.35 - 2.45	< 0.0001
Multivariate	**Variables**	**OR**	**95% CL**	***p***
	Age (per 10 years)	1.33	0.75 - 2.36	0.33
	Intra operative complications	26.3	3.62 - 191	0.001
	Blood loss (per 200 mL)	1.13	0.81 - 1.58	0.48

Table 2: Predictive factors of surgical conversion to open surgery in uni and multivariate analysis.

Univariate	Variables	OR	95% CL	*Wald chi-square p-value*
	Age (per 10 years)	1.30	0.93 - 1.86	0.14
	ASA score 2 vs. 1 3 vs. 1	1.23 2.00	0.40 - 3.80 0.53 - 7.60	0.55
	Diabetes mellitus	1.64	0.55 - 4.87	0.38
	Charlson comorbidity index (n = 95) 2 vs. 0-1 ≥ 3 vs. 0-1	1.47 1.50	0.30 - 10.7 0.32 - 10.8	0.89
	BMI (per 5 kg/m²)	1.24	0.85 - 1.80	0.26
	Operative time (n=108) (per 60 min)	1.57	1.05 - 2.39	0.03
	Blood loss (n=89) (per 200 mL)	1.14	0.98 - 1.35	0.11
	Intra operative complications	2.80	0.99 - 7.88	0.05
	Non expert surgeon	2.52	1.00 - 6.30	0.049
Multivariate	**Variables**	**OR**	**95% CL**	***Wald chi-square p-value***
	Intra operative complications	2.70	0.94 - 7.75	0.06
	Non expert surgeon	2.44	0.96 - 6.21	0.06

Table 3: Predictive factors of any grade of postoperative complications in uni and multivariate analysis

Univariate	Variables	HR	95% CL	*p*
	T	1.67	0.74 - 3.78	0.2165
	N	5.63	2.05 - 15.5	0.0008
	M	5.85	2.39 - 14.3	0.0001
	Fuhrman grade	2.48	1.33 - 4.60	0.0040
	Histological subtype			
	Papillary vs. clear cell	0.82	0.27 - 2.46	0.7259
	Chromophobe vs. clear cell	0.50	0.07 - 3.78	0.5015
	Positive margins	0.97	0.13 - 7.24	0.9739
	ECOG 1 vs. 0	2.24	0.88 - 5.69	0.0886
	2 vs. 0	1.32	0.17 - 10.4	0.7931
	Conversion to open surgery	1.46	0.56 - 3.76	0.4354
	Intra operative complication	1.11	0.37 - 3.29	0.8560
	Post operative complication	1.88	0.76 - 4.68	0.1734
	Tumor size	1.06	0.79 - 1.42	0.6746
	Blood loss (per 200 mL)	0.91	0.69 - 1.19	0.4893
	Operative time (per hour)	1.08	0.71 - 1.64	0.7227
Multivariate	**Variables**	**HR**	**95% CL**	***p***
	N	2.69	0.95 - 7.62	0.0614
	M	4.08	1.63 - 10.2	0.0026
	Fuhrman grade	2.42	1.21 - 4.84	0.0126

Table 4: Predictive factors of local recurrence and/or progression in uni and multivariate survival analysis

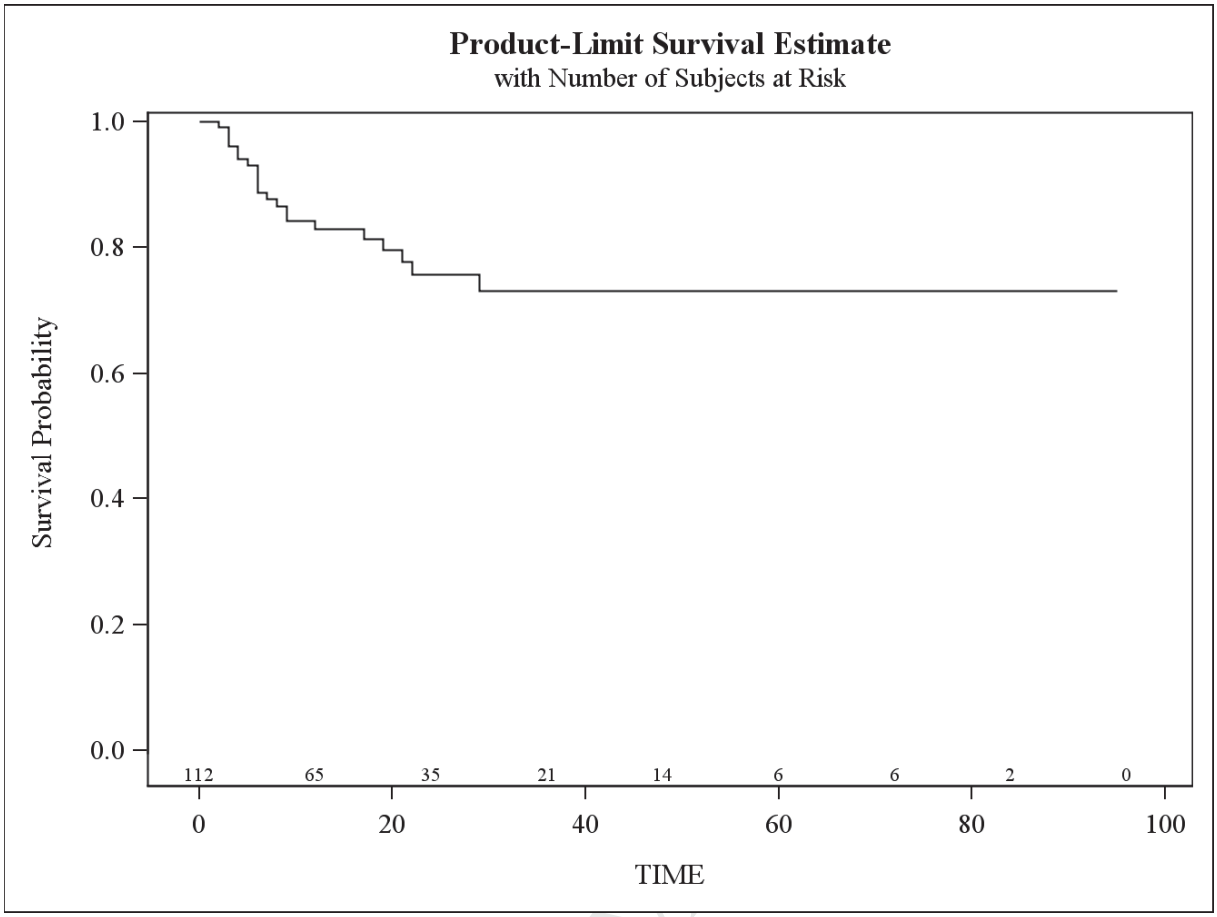

Figure 1: Kaplan-Meier survival estimate for progression-free survival (months).