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ORIGINAL ARTICLE

Predictive and prognostic effect of inflammatory lymphadenopathies in renal cell carcinoma

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Abstract

Purpose A significant proportion of patients affected by renal cell carcinoma (RCC) shows a suspicious lymph node involvement (LNI) at preoperative imaging. We sought to evaluate the effect of lymphadenopathies (cN1) on survival in surgical RCC patients with no evidence of LNI at final pathology (pN0).

Methods 719 patients underwent either radical or partial nephrectomy and lymph node dissection at a single tertiary care referral centre between 1987 and 2015. All patients had pathologically no LNI (pN0). Outcomes of the study were cancer-specific mortality (CSM) and other-cause mortality. Multivariable competing-risks regression models assessed the impact of inflammatory lymphadenopathies (cN1pN0) on mortality rates, after adjustment for clinical and pathological confounders.

Results 114 (16%) and 605 (84%) patients (16%) were cN1pN0 and cN0pN0, respectively. cN1pN0 patients were more frequently diagnosed with larger tumours (8.4 vs. 6.5 cm), higher pathological tumour stage (pT3–4 in 71 vs. 36%), higher Fuhrman grade (G3–G4 in 64 vs. 31%), more frequently with necrosis (75 vs. 44%), and distant metastases (33 vs. 10%) (all $p < 0.0001$). At univariable analysis, inflammatory lymphadenopathies resulted associated with worse CSM (HR 2.45; $p < 0.0001$). However, at multivariable analysis, inflammatory lymphadenopathies were not an independent predictor of CSM (HR 0.81; $p = 0.4$). The presence of metastases at diagnosis was the most important factor affecting CSM (HR 6.54; $p < 0.0001$). This study is limited by its retrospective nature.

Conclusions In RCC patients, inflammatory lymphadenopathies (cN1pN0) are associated with unfavourable clinical and pathological characteristics. However, the presence of inflammatory lymphadenopathies does not affect RCC-specific mortality.

Keywords Renal cell carcinoma · Lymphadenopathy · Lymph node invasion · Lymphadenectomy · Lymph node dissection

Introduction

Patients affected by renal masses are usually staged with computed tomography (CT) or magnetic resonance imaging (MRI) when a surgical treatment is planned [1–3]. A significant proportion of these patients shows a suspicious lymph node involvement (LNI) at preoperative staging [4–6].

However, imaging is characterized by a poor accuracy for nodal metastases [4–7] and lymph node dissection (LND) is nowadays considered the most reliable and accurate staging procedure in the renal cell carcinoma (RCC) setting [8–11]. Indeed, the concordance between clinical suspicion and pathological confirmation of node positive disease is low, ranging from 20 to 42%, with a positive predictive value ranging from 33 to 56% [5, 7, 12].

Fabio Muttin and Angela Pecoraro have equally contributed.

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The relationship between local and systemic inflammation and oncologic outcomes in RCC patients is under debate [13]. Similarly, it is likely that inflammatory lymphadenopathies (cN1pN0) may be associated with a more aggressive disease or with the patient's health or performance status, as well. However, no study has ever tested before the effect of inflammatory lymphadenopathies on RCC survival outcomes. To overcome this issue, we decided to assess the prognostic role of lymphadenopathies in RCC patients elected for surgical treatment with pathologically no LNI, namely, cN1pN0 patients.

Materials and methods

Study population

The present study relied on a prospectively maintained institutional database of patients elected for surgical treatment for renal masses at a single tertiary care European centre between 1987 and 2015. The study was undertaken with the approval and oversight of the institutional ethics committee review board. For the purpose of the study, we exclusively focused on patients with pathologically no LNI, namely, pN0 patients. Before surgery, each patient included in the analyses was staged with contrast-enhanced CT or MRI of the abdomen, regardless of RCC characteristics.

Clinical and pathological staging evaluation

Clinical and pathological tumour size was defined as the greatest tumour diameter in centimetres at preoperative imaging and final pathology, respectively. Clinical and pathological nodal stages were assigned according to the 2017 American Joint Committee on Cancer staging manual [14] and classified as cN0 vs. cN1 and pN0 vs. pN1, respectively. Cases occurred before the introduction of the aforementioned classification were reclassified. Clinical positive nodal stage (cN1) was assigned to all cases with evidence of loco-regional lymphadenopathies, defined as a minimum nodal diameter of 10 mm at preoperative CT or MRI. Fat tissue containing lymph nodes was put into separate containers per region of excision and fixed in 10% buffered formalin. All blocks were embedded in paraffin, cut into 3 mm thickness slices, and stained with haematoxylin–eosin. All surgical specimens were examined by dedicated genitourinary pathologists. For the purpose of the study, cN1pN0 patients were considered harbouring inflammatory lymphadenopathies, under the assumption that lymph node enlargement not attributable to RCC metastasis is due to reactive inflammatory changes [7, 15]. Lymphadenopathies due to haematological disorders (e.g., lymphoma) were excluded from the study.

Surgical template

Patients were treated with either radical or partial nephrectomy and lymph node dissection (LND). Lymphadenopathies have been systematically removed. According to clinical characteristics and surgeon's preference, overall LND template could be limited, side-specific, or extended [9]. Limited LND consisted of removal of lymphadenopathies only. Side-specific LND included hilar region plus, on the right side, precaval nodes or, on the left side, para-aortic nodes, from the adrenal vein to the level of aortic/caval bifurcation. Extended LND included regional LND plus, on the left, para-aortic and preaortic nodes from the crus of the diaphragm to the aortic bifurcation and, on the right, retro- and precaval nodes from the adrenal vein to the level of caval bifurcation. Interaortocaval nodes were always removed when an extended LND was sought. Loco-regional lymphadenopathies were pathologically assessed separately when additional nodes were removed [12].

Outcomes of the study

The primary endpoint of interest was cancer-specific mortality (CSM), defined as mortality due to kidney cancer. The secondary endpoint was other-cause mortality (OCM), defined as mortality due to a cause other than kidney cancer. Cause of death was defined according to death certificates or physician charts.

Covariates

Covariates consisted of age at diagnosis, gender (male vs. female), Charlson comorbidity index (CCI) [16], American Society of Anaesthesiologist score (ASA), Eastern Cooperative Oncology Group Performance Status (ECOG), year of surgery, presence of either local or systemic symptoms, preoperative serum haemoglobin (Hb; g/dL), clinical nodal stage (cN), clinical distant metastasis stage (cM), number of lymph nodes removed, pathological tumour size, pathological tumour stage (pT), and presence of tumour necrosis.

Statistical analyses

Statistical analyses as well as reporting and interpretation of the results were conducted according to established guidelines [17] and consisted of three steps.

First, medians and interquartile ranges (IQR) or frequencies and proportions were reported for continuous or categorical variables, respectively. Mann–Whitney and Chi-square tests were used to compare the statistical

significance of differences in the distribution of continuous and categorical variables, respectively.

Second, cumulative incidence smoothed plots were generated to simultaneously depict the 10-year CSM and OCM rates in the overall population and according to cN status.

Finally, univariable and multivariable competing-risks regression models were used to assess the impact of inflammatory lymphadenopathies on CSM and OCM, after adjustment for clinical and pathological confounders.

All statistical tests were performed using the RStudio graphical interface v1.1.453 for R software environment v.3.3.3 [18] with the following libraries, packages, and scripts: Hmisc, plyr, cmprsk, rms, stats, and graphics. All tests were two-sided with a significance level set at $p < 0.05$.

Results

Patients' characteristics

Overall, descriptive characteristics of the 719 cN0-1pN0 RCC patients included in the study are shown in Table 1. 114 (16%) and 605 (84%) patients were cN1pN0 and cN0pN0, respectively. Overall, the median yield of lymph nodes removed was 6 (IQR 3-10) and cN1pN0 patients were more likely to have more extended LND than the cN0pN0 counterpart ($p = 0.001$). A higher frequency of systemic symptoms and metastatic disease at diagnosis was found in cN1pN0 patients (all $p < 0.0001$). cN1pN0 patients usually had larger tumours at final pathology and higher pathologic tumour stage (all $p < 0.0001$). Moreover, cN1pN0 cases were more frequently diagnosed with higher Fuhrman grade and with tumour necrosis (all $p < 0.0001$).

Survival analyses

Median follow-up among survivors was 77 months. Overall, 265 (37%) deaths were recorded during the study period, 152 (21%) occurred due to kidney cancer and 113 (16%) due to other cause. The 10-year CSM and OCM rates were 21.6 and 14.2% in cN0pN0 and 47.4 and 15.5% in cN1pN0 subgroup, respectively (Supplementary Figure 1).

Table 2 reports the multivariable competing-risks analysis with respect to CSM and OCM. The presence of inflammatory lymphadenopathies resulted associated with worse CSM at univariable analysis (HR 2.45; 95% CI 1.68–3.57; $p < 0.0001$). However, after adjustment for all possible confounders, inflammatory lymphadenopathies failed to reach the independent predictor status (HR 0.81; 95% CI 0.52–1.27; $p = 0.4$). In addition, OCM was found affected by inflammatory lymphadenopathies neither at univariable (HR 0.81; 95% CI 0.43–1.52; $p = 0.5$) nor at multivariable (HR 1.1; 95% CI 0.53–2.28; $p = 0.8$) analysis.

Finally, cM1 stage and CCI were the main predictors affecting CSM and OCM at multivariable analysis, respectively.

Discussion

Nodal involvement is one of the utmost important factors influencing the prognosis of patients diagnosed with RCC, regardless of systemic metastasis status [19–21]. In the past, several investigations have noted a scarce concordance between the clinical suspicion and the pathological confirmation of LNI [7, 12]. As it is known, inflammation has a pivotal role at each step of cancer biology: cancer-related inflammatory microenvironment triggers cell-malignant conversion, local invasion, and distant metastases [22]. In this context, inflammatory lymphadenopathies (cN1pN0) may, for instance, be associated with a more aggressive disease or with the patient's general health status. However, no study has ever tested before the effect of inflammatory lymphadenopathies on RCC survival outcomes.

Under these premises, we evaluated the prognostic value of lymphadenopathies at preoperative imaging (cN1) in RCC patients submitted to LND at the time of surgery with no LNI at final pathology (pN0), regardless of the presence of metastatic disease. For this purpose, we hypothesized that cN1 status is associated with worse CSM in pN0 RCC patients treated with either radical or partial nephrectomy and LND.

CT of the abdomen is commonly used for the detection of lymph node metastases of RCC; however, it is burdened by high rates of false-positive and false-negative results [4–6, 12]. In our pN0 cohort, preoperative CT or MRI revealed 114 (16%) patients showing at least one enlarged lymph node suspected for LNI (cN1). Several series have evaluated the likelihood of metastatic nodal disease based on radiologic lymph node size greater than 1 cm. In a study on the accuracy of CT for detecting regional LNI, Studer et al. found a 42% concordance rate between clinical and pathological N1 status [7]. Furthermore, in our previous report, LNI was pathologically confirmed in less than 30% of patients with clinical suspicion of LNI [12]. Consequentially, several predictive models were developed to predict pathologically positive lymph nodes, thus reducing false-positive or false-negative results [10, 23–26]. Recently, Gershman et al. demonstrated that the only maximum lymph node short diameter at imaging had excellent predictive performance on pN1 disease [27]. The area under the receiver operating characteristic curve (AUC) of such a predictor was 0.84. In this series, the observed percentage of lymph node metastases was 20, 29, and 90% for lymph nodes 7, 10, and 30 mm in short-axis size, respectively. Considering the cT stage, the observed percentage of lymph node metastases was 1, 33,

Table 1 Descriptive characteristics of 719 patients treated with surgery for pN0 renal cell carcinoma at a single European institution between 1987 and 2015, according to the presence of lymphadenopathies at preoperative imaging

Variables	Overall population ($n=719$)	cN0 ($n=605$, 84%)	cN1 ($n=114$, 16%)	p value
Age, years				0.2
Median	60	60	63	
IQR	52–69	51–68	54–71	
Gender				0.2
Male	529 (74)	451 (75)	78 (68)	
Female	190 (26)	154 (25)	36 (32)	
BMI, kg/cm^2				0.9
Median	25.3	25.2	25.5	
IQR	23.1–27.7	23.1–27.7	22.8–27.7	
CCI				0.8
0	367 (51)	306 (51)	61 (54)	
1	180 (25)	153 (25)	27 (24)	
2	98 (14)	85 (14)	13 (11)	
3	44 (6)	35 (6)	9 (8)	
≥4	30 (4)	26 (4)	4 (4)	
ASA				0.001
1	167 (23)	149 (25)	18 (16)	
2	375 (52)	317 (52)	58 (51)	
3	164 (23)	132 (22)	32 (28)	
4	10 (1)	4 (1)	6 (5)	
5	1 (0)	1 (0)	0 (0)	
ECOG				0.03
0	216 (30)	190 (31)	26 (23)	
1	384 (53)	320 (53)	64 (56)	
2	108 (15)	88 (15)	20 (18)	
3	7 (1)	4 (1)	3 (3)	
4	1 (0)	0 (0)	1 (1)	
Preoperative Hb, g/dL				0.005
Median	13.1	13.2	12.6	
IQR	11.6–14.4	11.7–14.5	10.9–13.9	
Clinical tumour size, cm				< 0.0001
Median	7	6.5	9	
IQR	5–9	5–9	6.8–11	
Clinical T stage				< 0.0001
cT1–T2	604 (84)	530 (88)	74 (65)	
cT3–T4	115 (16)	75 (12)	40 (35)	
Clinical M stage				< 0.0001
cM0	620 (86)	544 (90)	76 (67)	
cM1	99 (14)	61 (10)	38 (33)	
Local symptoms				0.1
No	449 (62)	386 (64)	63 (55)	
Yes	270 (38)	219 (36)	51 (45)	
Systemic symptoms				< 0.0001
No	622 (87)	537 (89)	85 (75)	
Yes	97 (13)	68 (11)	51 (45)	
Year of surgery				< 0.0001
1987–1990	76 (11)	71 (12)	5 (4)	
1991–1995	143 (20)	125 (21)	18 (16)	
1996–2000	127 (18)	117 (19)	10 (9)	
2001–2005	122 (17)	107 (18)	15 (13)	

Table 1 (continued)

Variables	Overall population ($n=719$)	cN0 ($n=605$, 84%)	cN1 ($n=114$, 16%)	p value
2006–2010	167 (23)	129 (21)	38 (33)	
2011–2015	84 (12)	56 (9)	28 (25)	
Lymph node yield, *n*				0.001
Median	6	5	7	
IQR	3–10	3–9	4–14	
Pathologic tumour size, cm				< 0.0001
Median	6.5	6.5	8.4	
IQR	5–9	4.6–8.5	6.5–11	
Pathologic T stage				< 0.0001
pT1–T2	423 (59)	390 (64)	33 (29)	
pT3–T4	296 (41)	215 (36)	81 (71)	
Pathologic M stage				< 0.0001
pM0	328 (46)	293 (48)	35 (31)	
pM1	31 (4)	18 (3)	13 (11)	
pMx	120 (17)	107 (18)	13 (11)	
Furhman grade				< 0.0001
G1–G2	461 (64)	420 (69)	41 (36)	
G3–G4	258 (36)	185 (31)	73 (64)	
Tumour necrosis				< 0.0001
No	366 (51)	337 (56)	29 (25)	
Yes	353 (49)	268 (44)	85 (75)	

Data presented as frequencies and percentages unless otherwise specified

IQR interquartile range, *BMI* body mass index, *CCI* Charlson comorbidity index, *Hb* haemoglobin, *ECOG* eastern cooperative oncology group performance status, *ASA* American Society of Anesthesiologists score

and 38% for cT1–2, cT3a, and cT3b–4, respectively. The final multivariable model consisted of maximum LN short-axis diameter (OR 1.19 per mm; 95% CI 1.13–1.25) and radiographic perinephric/sinus fat invasion (OR 44.64; 95% CI 2.51–794.32). This model predicted pN1 disease with an AUC of 0.85.

Inflammatory lymphadenopathies resulted associated with unfavourable clinical and pathological characteristics and also with a 2.4-fold higher CSM at univariable analysis ($p<0.0001$). However, after adjustment for all possible confounders, the presence of Inflammatory lymphadenopathies did not affect CSM ($p=0.4$) and failed to reach the independent predictor status of survival.

Our results are in accordance with those of Vasselli et al., who observed that the survival of 154 patients undergoing cytoreductive nephrectomy for metastatic disease with completely resected lymphadenopathy was similar to that of patients without preoperative lymphadenopathy [28]. Furthermore, a recent study evaluated whether LND was associated with survival outcomes among patients at increased risk of harbouring pN1 disease [29]. Among cN1 patients, LND was not significantly associated with development of distant metastases, kidney cancer-related mortality or all-cause mortality.

Instead, other studies showed strong differences in terms of cancer-specific survival (CSS) among cN1 patients. Lee et al. relayed on 440 M0 RCC patients undergone to LND at the time of surgery and reported 5-year CSS of 92.1 and 77.9% in cN0pN0 and cN1pN0 patients, respectively ($p<0.001$), demonstrating a worse prognosis for cN1 patients [20]. In another report on 564 non-metastatic RCC patients undergone to LND at radical nephrectomy, Babaian et al. evaluated survival outcomes stratified by clinical and pathological nodal status [26]. cN1pN0 patients experimented worse CSS with respect to cN0pN0 counterparts. This study found a significant higher percentage of cN1pN0 cases than in our series (37 vs. 16%, respectively) [26]. This finding might be related to different inclusion criteria: in our series, metastatic patients could also harbour a higher rate of lymph node metastases leading to a reduction of false-positive cases.

Other additional observations fuel the debate. In our cohort, cN1pN0 patients seem to be sicker and more symptomatic and more frequently harbour systemic disease at diagnosis with respect to cN0pN0 counterpart. This observation confirms that direct haematogenous dissemination without lymphatic invasion is preferential in the RCC setting and that lymph node enlargement is still secondary to inflammation,

Table 2 Multivariable competing risk regression analysis addressing the impact of inflammatory lymphadenopathies on CSM and OCM, after adjustment for clinical and pathological confounders

Predictors	MVA predicting CSM		MVA predicting OCM	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1 (0.99–1.02)	0.9	1.09 (1.06–1.11)	< 0.0001
Gender				
Male	1 (Ref)		1 (Ref)	
Female	0.69 (0.46–1.04)	0.08	0.95 (0.66–1.38)	0.8
CCI	1.02 (0.84–1)	0.8	1.21 (1.06–1.39)	0.006
Preoperative Hb	0.92 (0.84–1)	0.04	1.01 (0.91–1.13)	0.9
Year of surgery	0.95 (0.93–0.98)	0.0005	0.94 (0.91–0.97)	0.0001
Clinical N stage				
cN0	1 (Ref)		1 (Ref)	
cN1	0.81 (0.52–1.27)	0.4	1.1 (0.53–2.28)	0.8
Clinical M stage				
cM0	1 (Ref)		1 (Ref)	
cM1	6.54 (4.38–9.76)	< 0.0001	0.46 (0.2–1.06)	0.07
Lymph node yield	1.01 (0.98–1.04)	0.5	1.01 (0.97–1.05)	0.6
Pathologic tumour size	1.06 (1.01–1.12)	0.03	1.04 (0.97–1.1)	0.3
Pathologic T stage				
pT1–T2	1 (Ref)		1 (Ref)	
pT3–T4	1.82 (1.2–2.77)	0.005	0.88 (0.56–1.4)	0.6
Furhman grade				
G1–G2	1 (Ref)		1 (Ref)	
G3–G4	1.87 (1.22–2.88)	0.004	1.06 (0.61–1.85)	0.8
Tumour necrosis				
No	1 (Ref)		1 (Ref)	
Yes	1.19 (0.77–1.82)	0.4	0.83 (0.55–1.27)	0.4
Local symptoms				
No	1 (Ref)		1 (Ref)	
Yes	0.94 (0.65–1.35)	0.7	1.09 (0.75–1.57)	0.7
Systemic symptoms				
No	1 (Ref)		1 (Ref)	
Yes	1.28 (0.85–1.92)	0.2	1.28 (0.69–2.39)	0.4

HR hazard ratio, *CI* confidence interval, *CCI* Charlson comorbidity index

follicular hyperplasia and fibrosis, even in a large proportion of metastatic patients [12, 21, 25]. Moreover, we reported that inflammatory lymphadenopathies are associated with greater tumour size and adverse pathological features. These data are consistent with findings of the previous aforementioned reports analysing predictors of pN1 status. Therefore, unfavourable clinical and pathological characteristics seem being associated with both inflammatory lymphadenopathies and pathologically confirmed LNI. This finding is of paramount importance, since pathologically confirmed LNI is one of the most informative predictors of survival in the RCC setting, even in patients with distant metastases [21].

Finally, kidney cancer was the leading cause of death in the overall population, accounting for 10-year CSM of 24.7% with respect to OCM of 14.3%. These data underline the critical importance of an accurate assessment of CSM risk at clinical decision making, especially in patients with lymphadenopathies. Remarkably, despite inflammatory lymphadenopathies were deemed associated with adverse pathological tumour features and CSM at univariable analysis, they were not found as an independent predictor of worse CSM in multivariable model. Consequently, positive clinical nodal status should not be considered detrimental during the clinical decision-making process unless pathologically confirmed as nodal metastasis.

Some limitations to the current manuscript may apply. First, the study lacked a central scan review performed by independent radiologists. Specifically, preoperative CT or MRI techniques were not standardized, and it is possible that other specialists might have staged differently each case. Radiology re-review was not performed which could have affected the accuracy of cN staging. Second, it is possible that other CT scan-derived nodal information, such as number of clinically positive nodes, nodal size, nodal

contrast uptake, lack of hilar fat, diffusion weighted images and other type of MRI technique, such as lymph-tropic nanoparticle-enhanced MRI, might increase the sensitivity and specificity of the preoperative imaging, although these aspects could not be addressed in the current study population. Third, the wide time span of the study (29 years) can also be interpreted as a limitation, since improving CT or MRI technology might eventually influence the probability of lymph nodes metastases diagnosis, as highlighted by the higher percentage of cN1 cases diagnosed in the most recent years (Table 1). On the other hand, this is also a strength of the study due to the relatively long follow-up (median 77 months), especially given the fact that all our survival models are adjusted for year of diagnosis (Table 2). Furthermore, data regarding inflammatory indexes were not take into account in our study. This choice was justified by the fact that, although an association between inflammatory indexes and RCC prognosis has been proved, no international guidelines recommend their use at any step of the clinical decision-making strategy and, as outlined by the previous investigations, the inclusion of an inflammatory index into a predictive model results in a marginal, or even any, increase of the predictive accuracy [13]. Finally, due to the retrospective nature of the current manuscript, recommendations regarding the type and the extent of LND that should be performed cannot be provided. In addition, the surgeons' preference and the retrospective data collection from patients' medical records might have someway affected the accuracy of the variable depicting the extent of LND. Nevertheless, the inherent selection bias of multiple LND templates used is adjusted by the inclusion of the lymph node yield in the multivariable models.

Conclusions

Clinical suspicion of lymph node metastases at preoperative imaging in patients diagnosed with kidney cancer portends unfavourable clinical and pathological characteristics, even in patients with pathologically no lymph node invasion. Nevertheless, the presence of inflammatory lymphadenopathies does not independently affect RCC-specific mortality. In conclusion, a radiological suspicion of nodal metastases should not be considered as a poor prognostic factor, at least not until confirmation of nodal involvement at final pathology.

Authors' contributions RB: supervision and critical revision for important intellectual content. AB: supervision and critical revision for important intellectual content. UC: project development, data collection, data analysis, manuscript editing, supervision, and critical revision for important intellectual content. FC: data collection. FD: data collection. PD: data collection and manuscript editing. Alessandro Larcher: project development, data analysis, and manuscript editing. FM: supervision and critical revision for important intellectual content. FM: data collection, manuscript writing, and manuscript editing. AN: data collection. AP: data collection and manuscript writing. AS: supervision and critical revision for important intellectual content. FT: data collection

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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