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MANAGEMENT OF c/pT3A RENAL CELL CARCINOMA IN LIGHT OF EAU GUIDELINES

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Abstract
Background:
The management and staging of cT3a renal cell carcinoma with invasion of the perirenal fat (cT3a-PFI) are complicated by the absence of standard imaging protocols and ambiguity in surgical decision-making. This review aims to assess management strategies, focusing primarily on European and French recommendations.
Background : Diagnosis and management of perirenal fat invasion cT3a renal cell carcinoma (cT3a-PFI) are still challenging with no well-adopted imaging protocols and uncertain surgical decision-making. The purpose of this review is to examine this management strategy primarily based on European and French guidelines.
Methods:
A systematic literature search was conducted on PubMed using the terms "renal cell carcinoma," "cT3a," "pT3a," and "perirenal fat invasion." English articles published between 2000 and 2024 were considered. After screening for relevance, study design, and evidence level, 42 articles were shortlisted for analysis.
Results:
The findings indicate that patients with cT3a-PFI have better recurrence-free survival (RFS) and cancer-specific survival (CSS) than those with sinus or vascular invasion. But preoperative diagnosis is still challenging because imaging features, such as irregularity of tumor contour, are of poor specificity for tumors larger than 4 cm. For tumors ≤7 cm, PN has similar oncologic results with RN, but RN is preferred in the situation of large tumors for technical complexity and higher risk of positive margins. The improved prognosis of cT3a-PFI tumors ≤4 cm, however, speaks for potential reclassification within the TNM system.
Discussion:
Published series are generally retrospective and hence come with selection bias and impaired strength of results. Even in the wake of imaging and therapy progress, standard diagnostic criteria still remain a huge obstacle. More research should aim to promote improvement in surgery and investigate even more innovative avenues like radiomics and artificial intelligence. A personalized surgical plan based on tumor size and technical possibility is essential for optimal results in patients with cT3a-PFI renal cell carcinoma. Prospective studies will be required to overcome current shortcomings and enhance management techniques.

Key words: RCC, c/pT3a staging, Perirenal fat invasion, Surgery, Oncological outcomes

Introduction:

The diagnosis of kidney cancer can be complex, particularly when assessing peritumoral or perirenal fat infiltration. The 2017 TNM classification by the American Joint Committee on Cancer divides stage T3 into three substages: cT3a, cT3b, and cT3c .[1] Recently, the European Association of Urology (EAU) kidney cancer committee proposed a revision of this classification. However, the cT3a substage remains unchanged .[2] This TNM classification retains a well-established prognostic value. In the pT3a group, the 5-year and 10-year recurrence-free survival (RFS) rates are estimated at 66% and 53%, respectively.[3,4]

The objective of this literature review is to thoroughly examine the cT3a substage with perirenal fat invasion (cT3a-PFI), given the limited number of articles specifically addressing this topic. This substage is defined by invasion of the perirenal or, more precisely, peritumoral fat ,[5] a characteristic independent of tumor size. Indeed, the favorable outcomes reported in some studies for this stage explain the interest in its diagnostic and therapeutic management.

Patients and Methods: A literature search was conducted using PubMed with the following keywords: **"Renal cell carcinoma," "cT3a," "pT3a," "perirenal fat invasion," "diagnosis," "surgical management," and "prognosis."** The search was limited to studies published in English between 2000 and 2024. After screening the literature, **42 articles were selected based on their relevance, study design, and level of evidence**.

Results

In a retrospective series of 266 patients, Park et al. [6] reported that pT3a-PFI had a better RFS prognosis (73.4%) compared to sinus invasion (72.1%), combined PFI and sinus invasion (46.9%), and renal vein invasion (44.2%). The 5-year cancer-specific survival (CSS) rates were 91%, 93.5%, 69.1%, and 67.9%, respectively.

Building on these findings, Thompson et al. [7] demonstrated that tumors invading the renal sinus fat are more aggressive than those with perirenal fat involvement. These findings were further confirmed by Stout et al. [8] who observed a nearly 50% reduction in CSS in patients with vascular or sinus fat involvement compared to those with cT3a-PFI. Patients with cT3a-PFI also had a better disease-free survival (DFS) rate than those with thrombus. They also recommend the use of intraoperative ultrasound in cases of suspected fat involvement to preserve peritumoral fat before incising Gerota's fascia.

Furthermore, to differentiate cT1 from cT3a, the EAU panel mentions in the staging and classification guidelines section that an analysis of tumor contour irregularity on imaging could be a valuable tool to guide therapeutic decisions, as suggested by the study of Xu et al..[9] However, no information on the relevance of this tool is provided, and the topic is not addressed elsewhere in the guidelines, including the imaging section .[8] The analysis of this study concludes that tumor contour irregularity, along with other factors such as age and tumor size, are independent predictors of T3a upstaging in multivariate analysis. Moreover, the combination of these three variables improves the accuracy of this predictive model. [9] Nevertheless, as with any retrospective study, the exclusion of patients without digital imaging data could introduce selection bias. Tumor contour irregularity has also been mentioned in other studies, but its specificity remains low, except for tumors smaller than 4 cm .[5,10]

Despite advances in multidetector CT technology, the preoperative diagnosis of cT3a remains challenging .[5,10-13] Although these technologies offer low positive predictive value (PPV) ,[5,12] they achieve a good negative predictive value (NPV), approaching 90%. [5,14]This situation stems from the difficulty in definitively confirming tumor spread into the perirenal space, particularly into the fat. Typically, this manifests as thickening or infiltration of the perinephric fascia, visible as linear areas of soft tissue attenuation. However, this sign is nonspecific and can lead to false positives, potentially reflecting hemorrhagic, vascular congestion, or inflammatory phenomena, such as edema or even peritumoral fibrosis.[5,11,12] Other signs have been reported, such as the presence of a centimeter-sized nodule in the fat adjacent to the tumor, which can help differentiate cT1 and cT2 from cT3a. The specificity of this sign approaches 98%, although its sensitivity is low at 46%.[15]

In the TNM classification, renal capsule invasion is a key criterion for distinguishing between T2 and T3 stages .[16] It has been associated with an increased risk of T3a-PFI (5.9%), without increasing the risk of tumor recurrence .[11] Other series report rates of capsular invasion without cT3a-PFI ranging from 7.2% to 37.5%.[17,18] Recent radiomic techniques allow for better detection of capsular invasion, a well-established risk factor for cT3a-PFI.[19,20]

A retrospective study using MRI to explore these masses demonstrated that the integrity of the tumor pseudocapsule is a sign of the absence of cT3a-PFI fat invasion .[21] According to Hedgire et al. ,[14] MRI appears more specific (92%) but less sensitive (72%) than CT, which showed a sensitivity of 84% and a specificity of 56%. Additionally, MRI/CT correctly identified cT3a-PFI in 26 cases but overdiagnosed it in 29 cases .[14] Imaging also seems more specific for tumors

larger than 5.5 cm [22], and tumor size is correlated with the risk of cT3a-PFI .[23] However, other series, such as that of Renard et al., found no statistically significant difference in tumor size between T2 and T3a stages. In fact, in this latter study, 83% of cT3a-PFI cases were understaged (as T1 or T2).[5] A European multicenter study [4] revealed that nearly half of pT3a tumors had a diameter of less than 7 cm. Interestingly, these PFI-T3a tumors were associated with a better prognosis, particularly in terms of 5- and 10-year CSS, compared to tumors larger than 7 cm. Moreover, the overall prognosis of these pT3a-PFI tumors was comparable to that of pT2 tumors .[4] According to this study, for upstaged PFI-T3a tumors, each 1 cm increase in tumor diameter is associated with a 9% decrease in CSS .[4] Furthermore, for T3a tumors larger than 7 cm, the median overall survival (OS) is 54 months, with CSS rates of 46% at 5 years and 36% at 10 years .[4]

Regarding the treatment of c/pT3a-PFI, few studies have evaluated the oncological outcomes of surgical treatment for cT3a. Yim et al. [24] analyzed data from 157 patients treated with partial nephrectomy (PN) with a median follow-up of 26 months. The median tumor size was 7 cm, and the RENAL score was 9. They reported acceptable complication rates, with a 5-year RFS of 82.1%, a CSS of 93.3%, and an OS of 91.3%. Similarly, Tian et al.,[25] in a large retrospective study based on SEER data, included 7,127 cT3a patients, of whom 3,949 had cT3a-PFI, and 986 underwent PN while 2,963 underwent radical nephrectomy (RN). The oncological outcomes were comparable, highlighting the efficacy of conservative surgical treatment for this tumor subtype.

Thus, most series dealing with pT3a are actually cases of upstaged cT1-2 to pT3a, with upstaging rates varying widely from 4.1% to 14% .[19,26-29] Moreover, the EAU panel does not provide clear recommendations for the management of cT3 patients.[2] In this chapter, reference is made to a meta-analysis [30] (nine studies including 1,278 PN and 2,113 RN for RCC reclassified as pT3a and not cT3) and two retrospective studies .[31,32] This meta-analysis found no difference in terms of CSS, OS, cancer-specific mortality (CSM), or RFS. Therefore, PN can be considered a relevant alternative to preserve renal function, provided it is technically feasible .[30] Regarding the two retrospective studies evaluating the oncological outcomes of cT1 and cT2 patients reclassified as pT3a, and contrary to what was mentioned by the panel ,[2] the study by Patel et al. ,[31] which reported similar oncological outcomes between PN and RN, is actually more recent than that of Shah et al..[32] The latter study suggests that for cT1 tumors reclassified as pT3a, PN is associated with a significantly shorter RFS than RN. However, aside from the retrospective nature of the study and the lack of details on the different PN techniques

(enucleation or others), the authors did not evaluate the relationship between RFS and CSS, limiting the clinical conclusions that can be drawn.

Regarding the RCC committee panel of the AFU, the authors recommend RN even for small renal masses in cases of suspected cT3a tumors .[33] However, these recommendations are largely based on the same studies cited by the EAU ,[30-32] the results of which have already been discussed and questioned. Notably, the AFU panel also included another retrospective study,[34] which evaluated the impact of pT3a upstaging on OS and compared the oncological outcomes of PN to those of RN. The results demonstrated that PN does not compromise DFS or OS compared to RN, even for larger tumors.

Furthermore, studies favoring conservative treatment, showing no significant difference in oncological outcomes between PN and RN, remain in the majority. Three large multicenter studies have examined DFS primarily in T1, T2, and upstaged T3a stages.[19,28,29] Although the authors reported lower DFS rates for upstaged pT3a patients compared to cT1 patients, the type of surgery (RN or PN) had no significant impact on this risk.

Deng et al. [35] conducted a meta-analysis of 12 studies of moderate to high quality, including 14,152 patients (2,486 PN and 11,666 RN), evaluating the outcomes of pT3a treatment. While PN showed better results than RN in terms of renal function preservation, no significant difference was observed between PN and RN regarding OS, RFS, or CSS. However, a higher rate of positive margins was noted in the PN group (RR = 2.42; 95% CI: 1.25-4.68; P = 0.009) .[35]

In a recent study published in 2023, Tan et al. [36] compared the oncological outcomes of 121 cT1a patients, 4,884 cT1b patients, and 190 cT3a patients with tumors smaller than 4 cm who underwent PN, with a median follow-up of 64 months (43–94 months). The results showed no significant difference in 10-year overall mortality between cT1a and cT3a <4 cm stages, despite a higher rate of positive surgical margins in the latter.

The importance of considering tumor size has been documented by several studies. Veccia et al. [37] published a systematic literature review and meta-analysis, including 13 studies involving 21,869 cT1 patients, of whom 1,256 (5.7%) were upstaged to cT1/pT3a. Age, tumor size, and RENAL score were identified as predictive factors for stage progression. Moreover, the 5-year RFS was significantly lower in the group with stage progression (p = 0.02) .[35]

Fukui et al. [26] found no significant differences between upstaged pT3a and pT1 groups in terms of OS, DFS, or RFS. Only tumor size in multivariate analysis was significantly associated with pT3a upstaging .[26]

However, Hansen et al. found no statistically significant difference in CSM at 2 and 5 years among 5,232 cT3a patients (477 PN or RN: 4,755), including after matched analysis of 477 RN and 477 PN. Thus, neither tumor size nor T3a stage should be a barrier to PN. The indication should rather depend on technical feasibility, provided negative surgical margins can be achieved.

Moreover, Srivastava et al. [39] analyzed the oncological outcomes of upstaged pT3a patients after PN (1,579) and RN (10,250), evaluating OS and CSS with a median follow-up of 48 months. For upstaged cT1a patients, OS and CSS were better in the PN group. In contrast, for cT1b and cT2 (≤16 cm) patients, survival rates were similar between the two groups. A subgroup analysis of pT3a-PFI patients showed that those treated with PN had no significant decrease in OS or CSS.

Liu et al. [40] collected data from a retrospective study of 1,277 pT3a patients, of whom 200 were treated with PN. After a median follow-up of 65 months for the PN group and 60 months for the RN group, PN improved survival for pT3a patients with tumors smaller than 4 cm compared to RN. For tumors between 4 and 7 cm, there was no significant difference in survival between the two approaches.

Similarly, Becker et al. evaluated the oncological and functional outcomes of 91 patients with tumors ≥7 cm treated with PN, with upstaging to pT3a in 25% of cases. They concluded that PN is a viable option, comparable to RN, when technically feasible, to preserve renal function .[41] Likewise, Breau et al. reported equivalent oncological outcomes between 69 patients treated with PN, of whom 41% had pT3a tumors <7 cm and 7% had pT3a tumors ≥7 cm, and 207 patients treated with RN .[42]

Discussion:

The findings of this review highlight the complexities and challenges associated with diagnosing and managing cT3a-PFI renal cell carcinoma. In our clinical experience, the preoperative differentiation of cT3a-PFI from other stages remains one of the most challenging aspects of RCC management. The retrospective nature of most studies introduces potential selection bias, which may limit the robustness of the conclusions. Additionally, the lack of

standardized imaging protocols and the inherent challenges in diagnosing cT3a-PFI restrict the generalizability of the results across different clinical settings. Despite these limitations, several key insights emerge from the available evidence.

First, the prognostic significance of cT3a-PFI is well-established, with studies consistently reporting better RFS and CSS for these patients compared to those with sinus or vascular involvement. This underscores the importance of accurate preoperative staging and the need for a validated nomograms, or reliable imaging features, to differentiate cT1 from cT3a tumors. However, the specificity of these data remains low, particularly for tumors larger than 4 cm, highlighting the need for further research to refine diagnostic criteria.

Second, the role of surgical management in cT3a-PFI remains a topic of debate. While PN is a viable option for tumors ≤7 cm, offering comparable oncological outcomes to RN while preserving renal function, RN is preferred for larger tumors due to technical complexity and the risk of positive margins. The favorable prognosis of cT3a-PFI ≤4 cm suggests that these tumors may warrant reclassification within the TNM staging system, as their outcomes are comparable to those of cT1 tumors.

Finally, we acknowledge that the retrospective nature of most studies introduces potential selection bias, which may limit the robustness of the findings. Moving forward, prospective studies are urgently needed to refine surgical guidelines for cT3a-PFI. These studies should aim to establish standardized diagnostic criteria and provide high-level evidence to guide clinical decision-making. In our opinion, such research should also focus on the role of advanced imaging techniques, such as radiomics and artificial intelligence, in improving diagnostic accuracy.

Conclusion :

To address the diagnostic and therapeutic challenges of cT3a-PFI, we propose categorizing this condition into three groups based on tumor size. For tumors ≤4 cm, PN with wide excision of peritumoral fat should be prioritized, given their favorable prognosis, comparable to cT1 tumors. For tumors between 4 and 7 cm, PN remains an option within the limits of technical feasibility, with wide excision of perirenal fat. However, for tumors >7 cm, PN should only be considered in imperative cases, favoring radical nephrectomy RN due to technical complexity and the risk of positive margins. Furthermore, a reevaluation of the TNM classification for cT3a-PFI ≤4 cm seems warranted, given their favorable prognosis. Prospective studies are needed to validate this proposal and assess its impact on patient management. In conclusion, an

individualized and precise surgical approach remains key to success. After all, a well-informed surgeon is worth two!

Abbreviation :

TNM - Tumor, Node, Metastasis (classification system)

cT3a - Clinical stage T3a (tumor stage)

EAU - European Association of Urology

RFS - Recurrence-Free Survival

cT3a-PFI - Clinical stage T3a with Perirenal Fat Invasion

CSS - Cancer-Specific Survival

DFS - Disease-Free Survival

CT - Computed Tomography

PPV - Positive Predictive Value

NPV - Negative Predictive Value

MRI - Magnetic Resonance Imaging

OS - Overall Survival

PN - Partial Nephrectomy

RN - Radical Nephrectomy

SEER - Surveillance, Epidemiology, and End Results (program)

AFU - Association Française d'Urologie (French Association of Urology)

CSM - Cancer-Specific Mortality

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