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Radiation therapy in renal cell carcinoma

Francesca De Felice*, Vincenzo Tombolini

Department of Radiotherapy, Policlinico Umberto I "Sapienza" University of Rome, Viale Regina Elena 326, 00161, Rome, Italy

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ABSTRACT

Renal cell carcinoma (RCC) is classically regarded as extremely resistant to classical fractionated radiation therapy (RT). Nowadays, there is convincing data supporting RCC radiosensitivity to high fraction doses, which may represent an ideal issue for new treatment strategies in primary and oligometastatic RCC disease. This review discusses the role of RT in RCC and its potential therapeutic scenario focusing on the most interesting clinical trials.

1. Introduction

Traditionally, renal cell carcinoma (RCC) has been considered a radioresistant tumor and therefore radiation therapy (RT) was mainly confined in treatment of metastasis. New advances in RT techniques, including stereotactic irradiation, have made encouraging contributions in the oncologic scenario, opening up new opportunities in RCC management.

This review provides highlights in current RCC strategies to potentially suggest a more tailored treatment approach in clinical daily practice. We firstly summarized the main RCC characteristics and presented a historical overview of RT role in RCC management. Then, we focused on the stereotactic RT and its potential value in RCC treatment. A set of queries, like definitive treatment in primary lesion and oligometastatic disease, and the radiobiological rationale, was pre-formulated as the basis for discussion.

2. Literature search strategy

All the available literature, including abstracts and full text manuscripts, regarding RT and RCC was reviewed. PubMed search was performed up to April 2018 using the following combinations of research criteria: "radiation therapy", "radiotherapy", "stereotactic", "stereo body", "ablative", "surgery", "nephrectomy", "renal cell carcinoma", "kidney cancer", "metastatic", "palliative therapy". Only publications in English were retained. Reference lists of previously published consensus guidelines, reviews and meta-analyses were explored. Abstract from international meetings were included only if appropriate and sufficiently powered statistical data. The discussion is more focused on the most frequent histological variant, the clear cell RCC.

3. Overview

Cancer of the kidney represents a rare entity, accounting for approximately 3% of all new malignancies (National Comprehensive Cancer Network, 2017). The vast majority (more than 90%) of kidney cancers are classified as renal cell carcinoma (RCC), arising from the tubular epithelium (National Comprehensive Cancer Network, 2017). The classic presenting signs, including hematuria, abdominal pain and mass, has nowadays shifted into asymptomatic lesion, due to incidental discovery on abdominal computer tomography (CT) scan performed for other clinical reasons. Sometimes RCC can present with evidence of vascular tumor thrombus (National Comprehensive Cancer Network, 2017).

The recently released eighth edition of the American Joint Committee on Cancer (AJCC) staging manual, in the kidney section, introduces minimal modifications from the prior seventh edition (Rini et al., 2017). Changes include revision of primary tumor (T) category. The definition of T3a disease has been modified: i) the word "grossly" was eliminated from the description of renal vein involvement; ii) the "muscle containing" was replaced by "segmental veins"; iii) invasion of the pelvicalyceal system was added. The cut-off point greater than 7 cm still distinguishes T1 from T2. The nodal (N) classification remains based on regional involvement (N1) of renal hilar, caval (including

* Corresponding author.
E-mail address: francesca.defelice@uniroma1.it (F. De Felice).

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interaortocaval, pre-, para- and retro-caval) and/or aortic (including pre-, para- and retro-aortic) lymph nodes, as well as metastatic disease (M1) in case distant metastasis, mainly in bone, liver, lung and brain (however it should be reminded that unusual metastatic sites such as paranasal sinuses, skin and penis). Interestingly, consistent with previous TNM staging, no new prognostic factors have been assessed. Therefore, the stage groups remain unchanged and worst survival outcomes are principally attributable to invasion beyond Gerota's fascia (T4) or the presence of distant metastasis (M1). In stage IV disease (T4 N0-1 M0; T1-4 N0-1 M1), the 2-year survival rate is less than 10%, whereas it ranges from 70% to 90% in the other stages.

The TNM classification is paramount to make the best treatment decisions. Usually, surgical resection represents the standard of care in RCC patients with localized disease (stage I-III) (National Comprehensive Cancer Network, 2017). In selected patients, such as elderly and those unfit for surgery, active surveillance and ablative techniques, including cryo- or radiofrequency ablation, represent valid alternative strategies for RCC management (National Comprehensive Cancer Network, 2017). Stage IV disease is mainly managed by systemic therapy. Oligometastatic patients in good performance status might benefit from cytoreductive nephrectomy before systemic therapy (National Comprehensive Cancer Network, 2017). However, supportive care remains a mainstay of therapy for all patients with metastatic disease (National Comprehensive Cancer Network, 2017).

4. Conventional radiation therapy

RCC has traditionally been an exclusive preserve of the surgeon. Due to the assumption that RCC is a radioresistant tumor, radiotherapy (RT) has long been considered a futile approach to manage primary disease, whereas it is mainly prescribed to treat distant metastasis, especially brain and painful bone metastasis, with a palliative intent (National Comprehensive Cancer Network, 2017).

4.1. Neoadjuvant radiation therapy

The role of neoadjuvant RT as an additional component of treatment in primary RCC has been tested more than 40 years ago. In that time period, the growing interest in neoadjuvant RT was based on the well-established RT role in tumor-downsizing, as well as its ability to cause fibrosis with thickening of the tumor capsule and sclerosis of the small blood vessels, making surgical resection easier (Waters, 1935). Consequently, several prospective studies evaluated the use of neoadjuvant RT followed by nephrectomy versus nephrectomy alone in order to analyze its influence on prognosis (van der Werf-Messing, 1973; Juusela et al., 1977). But they failed to demonstrate a definite benefit in survival outcomes. Actually, in the early 1970 s, van der Werf Messing reported a series of 126 non-metastasized clinically operable RCC patients randomly treated either by nephrectomy (n = 62) or by neoadjuvant RT immediately followed by nephrectomy (n = 64) (van der Werf-Messing, 1973;). RT was delivered to a total dose of 30 Gy (2 Gy/fraction), mainly to preserve liver functionality, especially in case of RCC of the right kidney. Although neoadjuvant RT guaranteed a considerably better survival at 18 months in those patients with tumor infiltrating intrarenal or extrarenal veins and/or lymph vessels, there was no demonstrable 5-year survival improvement of neoadjuvant RT compared to radical surgery alone. Interestingly, neoadjuvant RT was associated with higher rate of radical surgical removal, resulting in lower metastasis incidence, delayed metastasis onset and better short-term prognosis. But results did not support preoperative treatment in patients with RCC limited to the kidney.

The value of neoadjuvant RT was also not confirmed in Juusela et al prospective trial (Juusela et al., 1977). Globally, 88 patients were randomized to receive neoadjuvant RT followed by nephrectomy after a three week interval (n = 38) and nephrectomy only (n = 50). RT total dose was 33 Gy (2.2 Gy/fraction). Contrary to expectations, neoadjuvant RT did not improve the 5-year survival, showing a rate of 47% in the neoadjuvant RT group and 63% in the surgery group (even if no statistically significant), and none of the sub-groups benefitted from it.

Therefore, due to the absence of any clear evidence, in term of prognosis, supporting the neoadjuvant RT use, its interest in clinical research practice declines over the time.

4.2. Adjuvant radiation therapy

Current guidelines have completely abandoned the routine indication of adjuvant RT following radical nephrectomy even in those patients with residual microscopic disease on the basis of data from trials in the 1970 s and 1980 s. To our knowledge, only two trials were prospective in design (Finney, 1973). In Finney et al clinical study, a total of 100 patients were randomly treated by surgery plus adjuvant RT (n = 51) and by surgery only (n = 49) (Finney, 1973). But results demonstrated that RT did not improve 5-year OS (36% versus 44%), as well as did not positively influence local recurrence and distant metastasis. In addition, after adjuvant RT, a considerable number of patients died from coincidental causes (19.6%), including radiation liver damage. Similar final data was also recorded by Kjaer et al, confirming the absence of adjuvant RT beneficial effect on survival and relapse rates with an unacceptable complication rate, especially gastrointestinal toxicity (44%) (Kjaer et al., 1987). Recently, a meta-analysis (735 patients) was conducted to assess the impact of adjuvant RT on clinical outcomes, including overall survival (OS), disease-free survival (DFS) and locoregional failure (LRF), compared with nephrectomy alone in localized RCC patients (Tunio et al., 2010). Adjuvant RT significantly reduced LRF (odds ratio [OR]: 0.476, 95% confidence interval [CI] 0.334-0.680) but had no effect on OS (OR:0.851, 95%CI 0.630–1.151) and DFS (OR:0.790, 95%CI 0.573–1.087). However this meta-analysis had several limitations. The trials' accrual period ranged from 1968 to 1999 and, thus, almost all of the trials included used outdated RT techniques (parallel-opposed fields). Two included trials also come before the linear accelerator era. A further limitation concerns the improper RT total dose: the mean dose prescribed was 48.22 Gy (24 Gy – 63 Gy). Moreover, only two studies were designed as prospective clinical trials, limiting the quality of data analysis. Last, definitive conclusions cannot be made because of the low number of patients.

Surely, further research – better if based on randomized clinical trials – is paramount in order to better the definition of the superiority of adjuvant RT over surgery only in high-risk RCC patients. Studies should include at least intensity modulated RT technique, as well as an appropriate dosing (50 Gy to the tumor bed and the regional lymph nodes; 60 Gy in case of residual disease).

4.3. Palliative radiation therapy

RCC patients are at significant risk (more than 30%) to develop distant metastasis (Flanigan et al., 2003). Bone metastasis are diagnosed in approximately 50% of cases, whereas brain metastasis may occur in approximately 10% of cases. In this setting of patients, the median survival time range from 6 to 12 months, with a 2-year OS rate of 20% (Flanigan et al., 2003). RT represents an effective treatment option, due to its ability to palliate bone pain and alleviate cerebral symptoms. The selection of the more appropriate RT technique, such as 3-dimensional conformal and stereotactic technique, is principally based on both patients' (performance status and co-morbidities) and metastasis' (number and volume of lesion) characteristics. Generally, metastatic disease is managed successfully with external beam RT, using traditional palliative dose and fraction schedule, including 30 Gy in 10 fractions or 20 Gy in 5 fractions.

In the last decade, there has been satisfactory success with stereotactic treatments in cranial and extracranial metastatic RCC. A recent