

Stage I clear cell sarcoma of the kidney: is it the time for a less intensive adjuvant treatment?

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Abstract: Clear cell sarcoma of the kidney (CCSK) is a rare type of renal tumor, comprising 2% to 5% of all primary renal tumors in children. Despite the label of “unfavorable” tumor, with recent multimodality treatment schedules, including radiotherapy and multi-agent chemotherapy, disease free survival rates approaching 80% can be achieved. Younger age at tumor diagnosis and advanced-stage disease represent adverse prognostic factors. Of note, as a consequence of oncologic therapies a number of surviving patients have suffered from late sequelae on the musculoskeletal, gastrointestinal, hepatic, endocrine and cardiovascular function, or developed second tumors. Improved survival rates and a deeper knowledge of iatrogenic complications have promoted the awareness of a sequential reduction of treatment intensity, at least for low-stage CCSK, above all focusing on the abolition of flank radiation therapy (RT). It is fundamental to recognize that the rarity of this tumor calls for international cooperation through controlled clinical trials, and without forgetting the key importance of a correct histological diagnosis and adequate surgical staging. The recent recognition of CCSK specific chromosomal translocation might help to guide targeted therapies complementary to conventional chemotherapy and radiotherapy.

Keywords: Clear cell sarcoma of the kidney (CCSK); pediatric renal tumor; Wilms tumor

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The article recently published in the *International Journal of Radiation Oncology Biology Physics* by Kalapurakal *et al.* reviewing outcomes of children with stage I clear cell sarcoma of the kidney (CCSK) treated in National Wilms Tumor Studies (NWTS) 1 to 5 has attracted a renewed attention to this topic (1).

The authors specifically focused on 53 tumors classified as stage I according to the NWTS-5 renewed staging criteria, and that were centrally revised by the panel of NWTS pathologists. Varying study-specific adjuvant chemotherapy regimens were applied, always after primary radical nephrectomy. Regimens variably included one to four drugs (vincristine, dactinomycin, doxorubicin, cyclophosphamide, and etoposide) according to the sequential protocols adopted during the years (2-6). The great majority of patients (46/53) received flank radiation therapy (RT) as recommended in all

NWTS protocols, at doses ranging between 10 and 36 Gy (median dose, 10.8 Gy). No patient suffered from tumor recurrence, achieving 100% disease-free survival (DFS) and 94% overall survival (OS) rates at a considerable median follow-up of 17 years. Of note, several patients have suffered from late therapy-related sequelae on the musculoskeletal, gastrointestinal, hepatic, endocrine and cardiovascular function, and most of them were ascribed to the RT by the authors themselves. Two patients died of complications related to a second myeloid leukemia.

CCSK is an uncommon type of childhood renal tumor (comprising 2-5% of all primary renal tumors in children) and it is observed most often under three years of age (7).

Since its recognition in the 70s as a separate entity from Wilms tumor, CCSK has been always regarded as a “high risk histology” or “unfavorable histology” tumor among

pediatric renal neoplasms (8). Accordingly, the treatment strategy for children with CCSK has usually followed the one for higher risk pediatric renal tumors, like diffuse anaplastic Wilms tumor, both across the International Society of Pediatric Oncology (SIOP) and the NWTs (now the Children's Oncology Group, COG) protocols. Of course one factor that prevented studies or trials specifically tailored on CCSK was its rarity.

Despite the label of “unfavorable” tumor, with modern multimodality treatment schedules, including radiotherapy and multi-agent chemotherapy, outcome of CCSK is reasonable. In a recent paper investigators from the SIOP Renal Tumor Study Group reported an event-free survival (EFS) and OS rates of 79% and 86%, respectively, for 191 patients with CCSK treated on SIOP 93-01 and 2001 protocols (9).

In the latest analyses of 14 CCSK cases treated in the ongoing TW-2003 protocol of the Associazione Italiana Ematologia Oncologia Pediatrica, we documented DFS and OS rates of 84% and 91%, respectively (two relapses occurred in one stage III and IV each; stage distribution was as follows: stage I, four cases; stage II, four cases; stage III, three cases; stage IV, three cases) (Fraia Melchionda, personal communication).

Despite this improved survival, there is still a considerable relapse rate especially in younger children and in patients with advanced-stage tumor (9-11).

Note to mention, recent reports from the SIOP and the NWTs groups have indicated that, following recent intensified upfront treatment, the pattern of relapses is changing, with brain metastases more common than the classical pattern of bone metastases (9-14).

An important and burning issue raised by Kalapurakal *et al.* concerns the indication to flank RT in children with low-stage CCSK. RT to the primary tumor bed in the flank was recommended as a part of the multimodality treatment regimen for all stages in NWTs 1-5 protocols, and no relapses were observed. Also among seven patients who did not receive any RT ignoring protocol guidelines, no relapse occurred at a median of 22 years.

Importantly, in the most recent SIOP experience the 5-year EFS rate was 71.5% in 80 children with stage I CCSK, of whom only two received RT (whereas flank RT was administered to 76% of patients with stage II, III, and IV) (9). On the other hand, it is key to observe that only two of 12 relapsing stage I tumors occurred in the local area of the primary tumor (neither none of the 10 stage II patients treated without RT, violating protocol recommendations,

experienced a local relapse).

The lack of correlation between the RT therapy dose and local relapse rate has been previously shown by the NWTs Group (15).

What we can infer basing on the cooperative therapeutic experiences on CCSK so far, is that chemotherapy including doxorubicin, and a treatment duration longer than six months, seemed to have contributed to improved survival (15,16); and—but with less evidence—that addition of an alkylating agent is likely to be helpful (9). Worth mentioning, the recent SIOP report showed almost no tumor volume reduction after pre-operative chemotherapy consisting of vincristine and dactinomycin (plus an anthracycline in six metastatic patients); partial and minor responses were observed in 36% of patients, stable or progressive disease in 31% and 33%, respectively (9).

Current international protocols share a backbone with doxorubicin, etoposide and an alkylating drug (either cyclophosphamide—like SIOP and COG do (9,12), or ifosfamide—like AIEOP). Vincristine is somehow adopted in all the protocols, however in different phases of the protocols and at various cumulative doses (being employed only as neoadjuvant treatment in SIOP and AIEOP). AIEOP and SIOP do use carboplatin as an additional drug. It has to be taken into account that less intensive chemotherapy is applied in SIOP 2001 protocol for children with stage I tumors (containing vincristine, dactinomycin and doxorubicin, and without flank RT as already mentioned).

In conclusion, the paper by Kalapurakal *et al.*—together with a parallel one from the SIOP Renal Tumor Study Group (9)—further helps towards the sequential reduction of treatment intensity for low-stage CCSK, above all focusing on the abolition of flank RT.

Whether it is already under evaluation the effect of omitting flank RT in stage I CCSK, we believe that further key question would be the field size of RT. We raise the question on whether we might limit RT exposure to the primary tumor extent alone instead of the entire flank.

It is fundamental to recognize that the rarity of this tumor calls for international cooperation through controlled clinical trials. We here remark the key importance of a correct histological diagnosis—confirmed by expert pathologists in the field of pediatric renal tumor—and an adequate surgical staging (including adequate lymph node sampling), which remain the mainstay of a good clinical protocol on CCSK.

The recognition of CCSK specific chromosomal

translocation might guide the development of targeted therapy in this tumor (17).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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