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Radiotherapy in nephroblastoma treatment: Insights from a retrospective study

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Abstract

Wilms tumor, or nephroblastoma, is the most common pediatric renal tumor and represents a therapeutic challenge due to its often advanced presentation in our Moroccan context. This retrospective study examines 31 cases treated at CHU Hassan II of Fez between January 2014 and December 2020, assessing the impact of radiotherapy in the management of this disease. Patients underwent a multimodal approach combining chemotherapy, surgery, and radiotherapy. The analysis of epidemiological, clinical, and paraclinical data highlights the key role of radiotherapy, mainly performed using 3D conformal techniques, with or without intensity modulation, in preventing local recurrences and controlling metastases. Although some treatment-related complications were observed, the results are comparable to international standards, with an encouraging overall survival rate. These findings underscore the importance of a personalized and multidisciplinary approach to nephroblastoma management

Keywords: Nephroblastoma; Pediatric Oncology; Radiotherapy; Treatment Outcomes; Wilms Tumor

1. Introduction

Nephroblastoma, also known as Wilms tumor, is the most common malignant renal tumor in children, accounting for over 80% of pediatric renal neoplasms and between 5% and 14% (1) of all childhood cancers. Ranked as the fourth most common pediatric malignancy after leukemia, lymphoma, and brain tumors, this cancer is characterized by its embryonic origin, involving a disruption in renal development. Epidemiological data indicate that nephroblastoma primarily occurs between the ages of 1 and 5, with a peak incidence observed between the second and third years of life (2).

Over the decades, the management of this disease has significantly improved due to advancements in therapeutic protocols, particularly those developed by the International Society of Pediatric Oncology (SIOP) and the National Wilms Tumor Study Group (NWTS). These protocols implement a multimodal approach combining neoadjuvant chemotherapy, surgery, and, in advanced cases or those with a high risk of recurrence, radiotherapy. Radiotherapy, through its ability to precisely target the tumor volume and treat microscopic residual disease, plays a crucial role not only in preventing local recurrences but also in controlling metastases, particularly in the lungs and liver (3).

This retrospective study, conducted at CHU Hassan II of Fez, aims to assess the specific contribution of radiotherapy as part of a multimodal approach to nephroblastoma treatment. The objective is to confirm the added value of radiotherapy in local disease control and to identify the clinical and technical parameters influencing therapeutic outcomes and the occurrence of side effects.

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2. Methodology

This retrospective study focuses on 31 cases of nephroblastoma treated with radiotherapy between January 2014 and December 2020. The included patients met the following criteria: a diagnosis confirmed by histological examination after a radio-clinical evaluation, an age under 16 years, and a treatment plan incorporating radiotherapy as part of a multimodal approach. Data were collected from medical records archived in the radiotherapy and pediatric oncology departments and supplemented with information from the radiotherapy planning software. The collected data included epidemiological, clinical, and paraclinical characteristics of the patients, as well as therapeutic modalities and disease progression. Descriptive statistical analysis was performed to determine frequencies, means, and distributions of the different variables. Additionally, statistical tests were applied to assess associations between clinical, therapeutic, and outcome parameters, including the Chi-square test for qualitative variables and the t-test or ANOVA for quantitative variables, with a significance threshold set at $p < 0.05$.

3. Results

3.1. Epidemiological Characteristics

The patients' ages ranged from 9 months to 12 years, with an average age of 3.7 years and a peak incidence between 2 and 5 years. The sex distribution showed a female predominance, with 71% of cases being girls (F/M sex ratio = 2.4). Geographically, 71% of the patients were from the Fès-Meknès region. Additionally, approximately 25.8% of cases were from consanguineous marriages. (Table 1).

Table 1 Socio-demographic characteristics

Characteristics	**Number/percentage (%)**
Âge	
Mean	3,7 ans (9 mois – 12 ans)
Sexe	
• Female	22 (71 %)
• Male	9 (29 %)
Geographical origin	
• Fès	10 (32,2 %)
• Meknès	2 (6,5 %)
• Taounate	3 (9,7 %)
• Sefrou	3 (9,7 %)
• Boulemane	3 (9,7 %)
• Taza	1 (3,2 %)
• Khenifra	1 (3,2 %)
• Alhoceima	1 (3,2 %)
• Midelt	2 (6,5 %)
• Tinghir	1 (3,2 %)
• Errachidia	2 (6,5 %)
• Guercif	1 (3,2 %)
• Dakhla	1 (3,2 %)
Medical coverage	
• RAMED	21 (67,8 %)

• CNSS	5 (16,1 %)
• CNOPS	5 (16,1 %)
Consanguinity	
• present	8 (25,8 %)
• absent	23 (74,2 %)
Pathological history	
• Absent	30 (96,8 %)
• Present	1 (3,2 %)

3.2. Clinical Presentation and Diagnosis

The average consultation delay was 48 days, with most patients presenting with abdominal distension (71%) and a palpable abdominal mass (97%) (table 2). Abdominal ultrasound, performed on all patients, typically revealed a renal mass with characteristics suggestive of nephroblastoma.

Table 2 Distribution of patients according to clinical presentation

Clinical presentation	Number	Pourcentage
Abdominal mass	30	96,8%
Microscopic hematuria	5	16,1%
Fever	9	29%
Generalized poor health	15	48,4%
Lumbar tenderness	18	58,1%
Hypertension	2	6,5%
Collateral venous circulation	2	6,5

Ultrasound revealed a left-sided location in 16 patients (52%), a right-sided location in 13 patients (42%), and bilateral involvement in 2 patients (6%).

The abdominal-pelvic CT scan performed on all patients confirmed the presence of a left nephroblastoma in 16 patients, the largest measuring 17x12.4x11.3 cm, a right nephroblastoma in 13 patients, the largest measuring 14x14x10.4 cm, and bilateral involvement in 2 patients. Nephroblastomas were located at the upper pole in 16 patients (51.6%) and at the lower pole in 15 patients (48.4%).

Table 3 CT scan characteristics of the mass

Tumoral characteristics	Number	Pourcentage
Well-defined mass	22	71%
necrosis	21	67,7%
Kysts	14	45,2%
Calcifications	8	25,8%
Deep lymphadenopathy	14	45,2%
Hepatic metastasis	2	6,5%

The thoraco-abdominopelvic CT scan was performed on all patients as part of the staging workup. It revealed pulmonary micrometastases in 9 patients (29%), hepatic metastases in 2 patients (6.5%), vascular extension in 3 patients (9.7%) with thrombosis of the inferior vena cava (IVC) and renal vein, and adrenal involvement in 4 patients (12.9%).

Bone scintigraphy was performed in 6 patients, revealing bone metastasis in 1 patient (3.2%).

3.3. Histopathological prognostic data

The SIOP classification allowed for the distinction of 2 prognostic groups to guide adjuvant treatment: intermediate risk in 14 cases (45.2%) and high risk in 17 cases (54.8%). Among the 14 patients with intermediate-risk tumors, 9 cases (29%) had mixed nephroblastoma, while 5 had regressive nephroblastomas (16.1%). For high-risk tumors, 10 patients were blastemal (32.3%), and 7 had diffuse anaplasia (22.6%).

3.4. Treatment Modalities

The treatment protocol included neoadjuvant chemotherapy, followed by surgery, and then radiotherapy.

The neoadjuvant chemotherapy regimen was based on the combination of two drugs: vincristine and actinomycin D. In metastatic cases, a third drug, Adriamycin, was added.

The number of chemotherapy cycles was 4 for localized forms and 6 cycles for metastatic forms.

In our series, 16 patients were treated according to the localized protocol (51.6%), while 14 received the metastatic protocol (45.2%).

All patients underwent total ureteronephrectomy, extended via a transperitoneal approach. The time between the last neoadjuvant chemotherapy cycle and the surgical procedure was adhered to in 29 cases, ranging from 7 to 33 days, with an average of 13 days.

Adjuvant chemotherapy was administered to all patients (100%) according to the GFA Nephro-2005 protocol. Eleven patients were treated with a combination of Actinomycin, Vincristine, and Adriamycin (53.5%), while 20 patients (64.5%) received Cyclophosphamide, Adriamycin, Etoposide, and Carboplatin.

The time between surgery and the first radiotherapy session ranged from 26 days to 3 months, with an average of 45 days. Radiotherapy was mainly performed using three-dimensional conformational techniques (with or without intensity modulation) depending on the tumor's location and extent. The irradiated sites included: the ipsilateral flank in 14 patients (45.2%), the lungs and flank in 5 patients (16.1%), the lungs and lumbar spine in 1 patient (3.2%), and the abdomen in its entirety in 11 patients (35.5%) due to tumor rupture in 9 patients and residual disease in 3 others. Planning included the precise definition of target volumes: GTV (gross tumor volume), CTV (clinical target volume), and PTV (planned target volume).

The total dose varied depending on the extent, ranging from 10.5 Gy to 19.8 Gy for local treatment and from 10.5 Gy to 30 Gy for metastatic sites, with an average dose of 17.5 Gy.

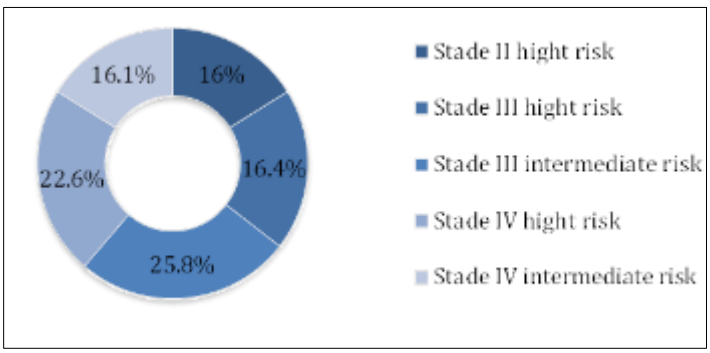

Figure 1 Distribution of patients according to the indication for radiotherapy

3.5. Evolution and complications

Therapeutic outcomes showed complete remission in 17 patients, partial remission in 4 patients, recurrence in 7 patients, and 10 cases of death. The mean overall survival at 5 years was 7.876 (+/-0.708). According to Kaplan-Meier curves, the mean progression-free survival was 8.664 (+/-0.627). (Figure 2-3)

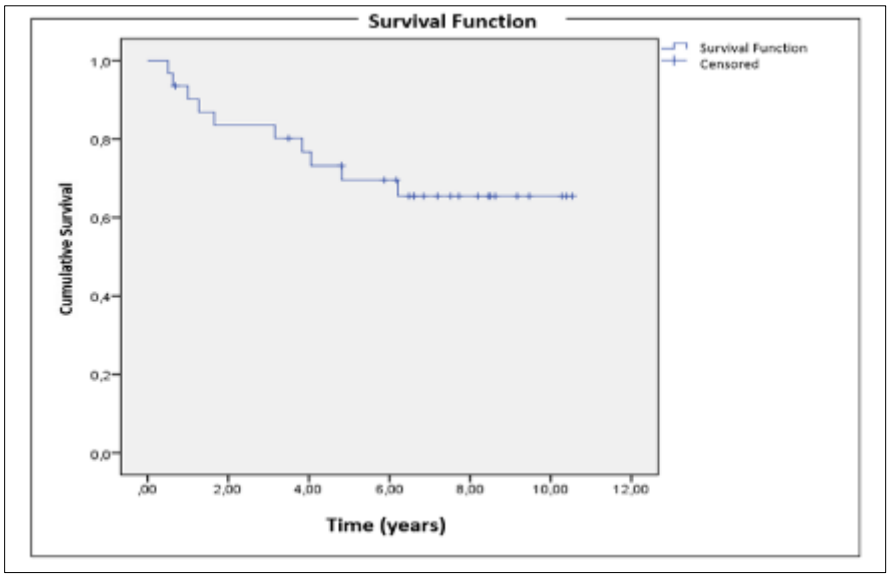

Figure 2 Overall survival estimated by Kaplan-Meier curves

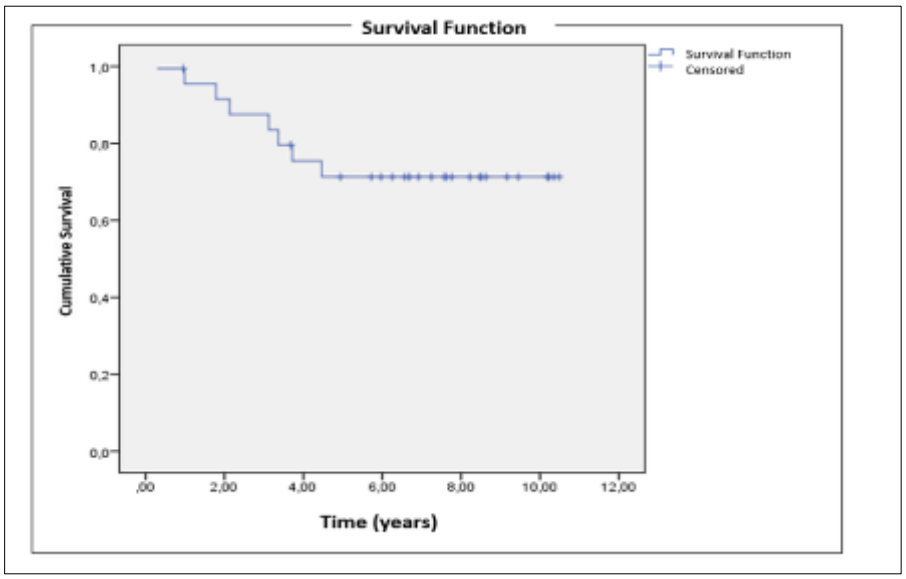

Figure 3 Progression free survival estimated by Kaplan-Meier curves

Early complications included bone marrow aplasia in 9.7% of patients and thrombocytopenia in 16.1%. Skin and mucosal complications were observed, with grade I radiomucitis in 9.7% of cases and grade I radiodermatitis in 6.5% of patients, as well as digestive issues such as constipation (9.7%), diarrhea (3.2%), and vomiting (12.9%). On the other hand, late complications were limited to growth disorders, noted in 12.9% of patients, with statural or staturo-ponderal delay in children under 5 years old who had received total abdominal irradiation.

4. Discussion

The incidence of nephroblastoma varies by region and ethnic origin, with a higher frequency among Black populations and a lower prevalence in Asia (4). In Morocco, data from the cancer registries of Casablanca, Rabat, and Marrakech

indicate a stable prevalence, with an average of 4 to 5 cases per year in our series at CHU Hassan II of Fez over a 7-year period. The median age at diagnosis is 3 years, consistent with the literature, and a slight female predominance is observed in our study (M/F sex ratio of 0.41). (5-6-7)

Although the majority of cases are sporadic, approximately 10 to 17% are associated with predisposing syndromes such as WAGR, Denys-Drash, or Beckwith-Wiedemann, which involve specific genetic alterations on chromosome 11 (8-9). These syndromes warrant close monitoring for early diagnosis. Our results confirm the importance of these factors in patient management and highlight epidemiological disparities influenced by socio-economic conditions and access to healthcare.

The average consultation delay in our study was one and a half months. This delay varies across studies, reaching up to two months in Ilhame B.'s series (10), with extremes ranging from 2 days to one year. In contrast, it was similar to ours (one and a half months) in Houmair Y.'s study (11), with an interval ranging from 10 days to 6 months.

In sub-Saharan Africa, consultation delays are generally longer, as illustrated by Diarra's series (12) in Bamako, where the average delay was 3 months. In some regions of West Africa, delays can be even longer (13)

This prolonged consultation delay may be explained by a lack of awareness about the disease and the low socio-economic status of the affected populations, leading to delayed medical consultation.

Nephroblastoma usually manifests in children under the age of 5 as an abdominal mass, often detected by parents during bathing or by a pediatrician during a routine physical examination. Although it is often asymptomatic, patients may present with abdominal pain, hematuria, and, in some cases, hypertension (14).

Additionally, patients may experience malaise, fever, weight loss, anorexia, or a combination of these symptoms. A varicocele due to tumor compression of the spermatic cord may also be observed (15).

In our series, the most common presenting symptom of nephroblastoma was an abdominal mass in 61.3% of cases. This finding aligns with studies by Houmair Y. (11) and Diarra (12), which reported abdominal distension as the primary warning sign in 66% and 61% of children, respectively.

According to the UMBRELLA SIOP 2016 protocol (72), magnetic resonance imaging (MRI) is the gold standard for a comprehensive evaluation of the abdominal cavity, from the hepatic dome to the pelvis, due to its excellent soft tissue resolution and the absence of ionizing radiation. For young children, a specific protocol may be used, which can include sedation. It is recommended to perform an MRI before a tumor biopsy, as it provides better tissue characterization and a more precise assessment of tumor extension both at diagnosis and during follow-up (16).

Abdominal computed tomography (CT) is considered a second-line imaging modality after ultrasound if MRI is unavailable. It helps confirm the location and appearance of the renal mass, identify potential liver metastases and tumor extension into renal vessels, and rule out other causes of renal masses (17). In our series, all patients underwent abdominal CT, which revealed characteristic images of nephroblastoma.

For staging purposes, thoracic CT complements standard chest X-ray and helps detect possible thoracic metastases that may not be visible on conventional radiography. In our series, thoraco-abdominal CT was performed for all patients and identified pulmonary metastatic lesions in nine cases.

Similar to the SIOP 2001 protocol, the UMBRELLA-SIOP-2016 protocol continues to recommend preoperative administration of actinomycin, vincristine, and doxorubicin for patients older than six months (18). In our series, induction chemotherapy was administered to nearly all patients (96.8%), except for one child who underwent immediate surgery. This was based on the GFA-Nephro-2005 protocol, derived from the SIOP 9 (2001) protocol and adapted to the African context.

Surgery is a cornerstone in the treatment of nephroblastoma. According to the European (SIOP) protocol, preoperative chemotherapy is administered to reduce tumor size and facilitate a cold excision, whereas in North America (NWTS), immediate surgery is preferred. The procedure also helps determine the surgical stage. The main risk is tumor rupture, with an incidence of 9.7% in the AREN03B2 study, compared to 2.8% to 6% in SIOP studies, likely due to tumor shrinkage and reduced vascularization after chemotherapy (18-19).

Nephroblastoma is highly radiosensitive and can be effectively treated with moderate doses of radiotherapy (15–30 Gy). In the 1960s, the combination of surgery and radiotherapy resulted in cure rates exceeding 50%, albeit with significant toxicity. The introduction of chemotherapy has optimized radiotherapy indications, reduced radiation doses, and improved survival rates. Advances in imaging and radiotherapy techniques have further enhanced treatment precision and radiation protection.

Between the SIOP-1 (1971–1974) and SIOP-2001 (2001–2016) protocols, radiotherapy utilization decreased from nearly 100% to 20–25%, alongside dose reductions. The UMBRELLA SIOP-RTSG-2016 protocol maintains similar indications while integrating technological advancements. In sub-Saharan Africa, access to radiotherapy remains limited, as observed in the GFAOP-NEPHRO study (20-21-22).

Radiotherapy plays a crucial role in nephroblastoma treatment by improving local control and targeting metastatic sites. Its indication depends on tumor stage, histology, and, more recently, molecular profiling. It is particularly beneficial for preventing local recurrences and managing pulmonary, hepatic, cerebral, and bone metastases (3).

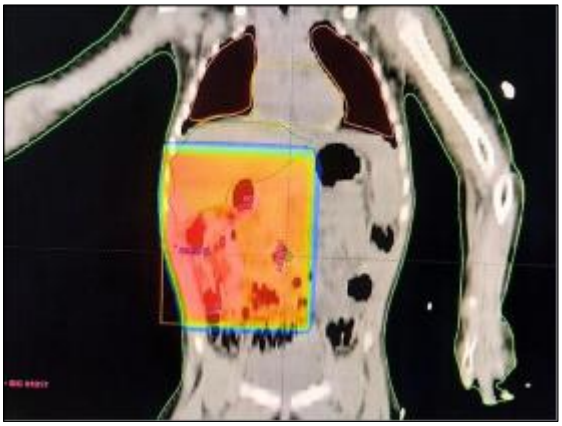

Figure 4 Right renal bed irradiation

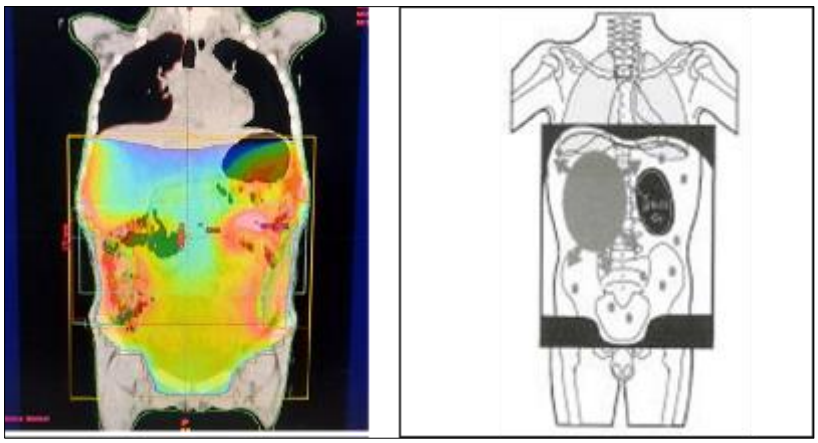

Figure 5 Total abdominal irradiation

The timing between nephrectomy and radiotherapy significantly impacts therapeutic outcomes. Historically, initiating treatment within 10 to 14 days post-surgery has been associated with improved overall survival, though some studies have not confirmed this correlation (21). The UMBRELLA-SIOP 2016 protocol recommends an interval of 2 to 4 weeks. However, in practice, delays often occur due to the workload of specialized centers and the time required to obtain histological results.

Radiotherapy indications vary according to disease stage and treatment response. It is prescribed for high-risk tumors, advanced stages, and residual metastases after chemotherapy. The most frequently irradiated sites include the

ipsilateral flank, abdomen, and lungs (Images 1-2). Advances in techniques, particularly three-dimensional conformal radiotherapy, have optimized tumor targeting while preserving healthy tissues, reducing toxicity, and improving clinical outcomes.

Early complications of radiotherapy include bone marrow aplasia, thrombocytopenia, radiomucositis, and grade I radiodermatitis, as well as digestive disorders such as nausea, vomiting, constipation, and colic. Their frequency can be reduced by improving radiotherapy techniques and adjusting fractionation. Late complications, though rarer but potentially severe, impact long-term survival, increasing the risk of chronic diseases and secondary cancers, particularly sarcomas, breast cancer, lymphomas, and leukemia, with a cumulative incidence of 2 to 3% at 30 years.

The risk of cardiovascular complications is higher after left flank irradiation, promoting coronary artery disease, pericarditis, and valvular disease, especially in young patients and women. Renal function is often reduced, with an increased risk of end-stage renal failure, particularly after bilateral Wilms tumor. In children, irradiation can lead to growth retardation, bone abnormalities, and breast hypoplasia, especially before the age of five. Pulmonary complications, such as fibrosis, affect approximately 5% of patients within 15 years of treatment. Finally, fertility may be impaired, particularly after total body irradiation and chemotherapy with alkylating agents. (22)

Wilms tumor is a curable disease in the majority of children, with a 5-year survival rate exceeding 90% for favorable histology cases in the United States. (2) Prognostic improvement is linked to treatment optimization, including reduced therapy duration and intensity. According to the SIOP-9 protocol, 5-year relapse-free survival and overall survival vary depending on stage and histology, ranging from 100% for low-risk stage I tumors to 64% and 79% for stage III tumors with unfavorable histology.

Metastatic Wilms tumors with unfavorable histology, particularly diffuse anaplastic forms, have a very poor prognosis, with a 5-year survival rate below 25%. Relapses occur in 20% of patients, primarily in the lungs (⅔ of cases), with a better prognosis for isolated forms (64% 3-year survival if only one lung is affected, compared to 32% if both are involved). Abdominal and lymph node relapses are rarer but have a poorer prognosis, while bone and brain relapses are particularly aggressive. In the SIOP-9 study, overall survival was 75%. In the series studied in Fès, overall survival was 67.7%, with 77.4% of patients in remission. Ten deaths were recorded, mainly due to pulmonary, abdominal, or contralateral relapses, as well as post-therapeutic complications. (23)

5. Conclusion

Radiotherapy appears to be a crucial element in the therapeutic strategy for Wilms tumor, particularly in ensuring local control and preventing metastases. The integration of advanced techniques allows for optimizing the balance between tumor efficacy and the preservation of healthy tissues. These results, in line with international studies, support the importance of a multidisciplinary approach to improve survival and quality of life for children with Wilms tumor.

Strengths and limitations of the study

Our study is one of the few Moroccan analyses on the role of radiotherapy in the treatment of Wilms tumor, providing valuable data on the epidemiological characteristics and therapeutic outcomes in the Fès-Meknès region. However, some limitations must be highlighted, including the small sample size, which limits the generalization of the results, as well as a selection bias related to the exclusive inclusion of patients requiring radiotherapy, leading to an overrepresentation of certain disease stages. Additionally, the presence of missing data and the loss of follow-up for some patients may affect the interpretation of the results. These factors emphasize the need for larger, multicenter studies to refine knowledge on Wilms tumor and optimize its management.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest related to this study.

Statement of ethical approval

All authors declare that the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Author Contributions

The role of each author in the design and writing of this article is as follows:

S.K ,Methodology, S.K and A.B; Software,S.K and A.B; Validation, S.K and A.B.; Formal Analysis, S.K and A.B.; Investigation, S.K and A.B, S.E M,W.H,FZ.F, Z.A and T.B.; Resources, all authors; Data Curation; Writing—Original Draft Preparation, S.K, Writing—Review and Editing, S.K and A.B, S.E M , Visualization, S.K and A.B, W.H,FZ.F, Z.A and T.B Supervision. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Data available upon request.

Statement of informed consent

The patients who participated in this study provided written informed consent.

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