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RUNNING TITLE:
Renal transplant in Wilms tumor

Timing of renal transplant in survivor children with relapse of Wilms tumor, a case series study

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Abstract
Introduction: Children with Wilms tumor can rarely experience late relapse of disease. Sometimes bilateral nephrectomy is necessary, as consequence, patient needs hemodialysis waiting for renal transplantation. The waiting time to transplantation after cancer has always been debated issue. **Case presentations**: We present two cases of late relapse of Wilms tumor underwent bilateral nephrectomy. Patient 1 was put in the attending list for renal transplant after 5 years to the stop treatment, attending the conventionally time; however she died before transplant because of complications in Sars-Covid-19 infection. Patient 2 underwent to renal transplant sooner compared to the conventional time, improving her quality of life and alive. **Conclusion**: If bilateral nephrectomy is necessary, in oncological patients, the timing of renal transplant should be discussed in multidisciplinary team. In our cases the different time to renal transplantation was associated to different outcome. Clinicians should have common lines about the time of renal transplantation in pediatric oncology, however a personalized planning could be suggested after discussion among specialists, evaluating case to case. The presented field needs more knowledge and further larger case series are necessary to evaluate outcome related timing of renal transplant; in this view collaboration between oncology centres is strongly required.

Introduction
Wilms tumor (WT) is the most frequent renal tumor in children, with a reported incidence of 9 cases per million per year in children under 15 years of age, the majority of them under 5 years [1]. With current treatments, 90% of patients proved to survive, even if the tumor was metastatic at diagnosis [2, 3]. Relapse occurred respectively in about 50% and in 15% of patients with unfavorable and favorable histology, more frequently in the first 2 years after diagnosis [2, 4]. Late recurrence (after 5 years from diagnosis) occurred in 0.5% of cases [5].
Children with end stage kidney disease (ESKD) should undergo renal transplantation as soon as possible to reduce the side effects of hemodialysis [6]. However, for children with diagnosis of tumor, different international guidelines suggest a waiting period (at least 2 years from the end of tumor treatment) before transplantation [7, 8]. However, different societies have recently suggested a case-by-case approach, based on individual experience and cancer characteristics [9]. Furthermore, in the past some authors proposed to avoid the 2 years' waiting time for patients with ESKD due to WT [10, 11]. Moreover, for the rare cases of late recurrence requiring bilateral nephrectomy as the final option due to disease and/or treatment, there are no clear recommendations about waiting time to transplantation. On the one hand, we have a late recurrent tumor that suggests a waiting approach and careful evaluation before transplantation, on the other hand we have a young patient that needs hemodialysis with its long-term side effects.
This article describes 2 cases of ESKD following bilateral nephrectomy due to late recurrence of WT that were put on renal transplantation waiting list at different times.

Case Report/Case Presentation
CASE 1
Female, 6 years old at diagnosis of stage III WT of left kidney, diffuse anaplasia at histology, and family history of renal polycystosis.
The patient underwent first line treatment according to the Italian protocol AIEOP TW 2003, regime D, including chemotherapy with vincristine (VCR), dactinomycin (ACTd), adriamicina (ADM), followed by left nephrectomy and radiotherapy, and a second time of chemotherapy with ifosfamide (IFO) + ADM, alternated with carboplatine (CBDCA) + vepeside (VP16), for a total of 34 week of treatment. At the end of treatment the patients was in complete remission of disease (CR).
Seven years after the first diagnosis, the patient had a relapse of the tumor in the contralateral kidney. The ultrasound scan, performed for abdominal pain, showed a mass adhering to the right kidney, complicated by intracaval thrombosis and acute kidney injury (shown in Fig. 1). Thoracic-abdominal CT scan was performed, showing the presence of a single pulmonary metastasis (shown in Fig. 2). In consideration of the late relapse, the patient was initially treated with chemotherapy according to the Italian protocol AIEOP TW 2003, regime E which plans to start with VCR, ACTd and

ADM, but ADM was omitted due to previous chemotherapy. After this first cycle, the patient experienced tumor rupture with consequent hemoperitoneum and the treatment was temporarily suspended. Upon clinical recovery (after 26 days), chemotherapy was administered for 5 weeks (VCR weekly and ACTd at week 1 and 3), then it was continued with one cycle of associated VCR, ACT-d and ifosfamide and 2 cycles of topotecan plus temozolamide (TOTEM). Concurrently, hemodialysis was started, followed by right nephrectomy and pulmonary metastasectomy. The patient achieved CR of disease.
Five years after the end of the second treatment, the patient was in CR of tumor with hemodialysis performed thrice a week. As a consequence of treatments, she developed heart disease. The patient was put in the waiting list for renal transplantation after 5 years in CR. However, she died before kidney transplantation as a result of complications due to Sars-Covid-19 infection.

CASE 2
Female, 4 years old at diagnosis of WT, stage IV, with multiple pulmonary metastases and inferior vena cava thrombosis. The patient was treated according to the Italian protocol AIEOP TW 2003, regime E, including chemotherapy with VCR, ACT-d, ADM, and surgery (right nephrectomy and pulmonary metastasectomy) followed by radiotherapy to the right abdomen. Histology described a triphasic WT with 50% residual live cells without anaplasia. At the end of treatment, 9 months after diagnosis, CR of disease was confirmed. Regular follow-up was carried out.
Late relapse occurred 14 years after the first diagnosis. Symptoms were fatigue and altered values of blood pressure. CT-scan (shown in Fig. 3) revealed the presence of a mass in the left kidney and multiple bilateral pulmonary nodules. A biopsy of the mass confirmed the relapse of WT in the left kidney, without anaplasia. The treatment was started according to SIOP Umbrella protocol including chemotherapy with the association of cyclophosphamide/ifosfamide, carboplatin and etoposide. After 4 cycles of chemotherapy, a partial response of the renal mass and a complete response of the pulmonary metastases were observed. Then treatment was continued with high-dose chemotherapy (melphalan) followed by autologous hematopoietic stem-cell transplant followed by nephron-sparing surgery. Histological examination confirmed the presence of post-chemotherapy regressive nephroblastoma, with 20% residual live tumor cells. According to the protocol, treatment should have been completed with radiotherapy to the lungs. However, considering the complete remission of the pulmonary metastases and the presence of concomitant heart disease (mild aortic insufficiency with reduction of left ventricular function), radiotherapy was not performed. Radiological evaluation at the end of treatment showed CR of disease.
At 4 months from the end of treatment, a relapse of disease was detected at CT-scan performed during the routine follow-up, which showed a residual left kidney parenchymal lesion and neoplastic thrombosis of the left renal vein. Second line treatment was carried out including 6 cycles of associated vincristine, irinotecan and temozolamide followed by left nephrectomy. Histology showed double localization of the tumor, with < 5% residual live tumor cells. At the end of treatment, CR of disease was confirmed and the patient underwent hemodialysis thrice a week.
At 20 months from the end of treatment, persisted CR and the case was discussed among oncologists and nephrologists, and it was decided to put the patient in the waiting list for renal transplantation. To date the patient is alive and wellness after the renal transplant that was performed at 39 moths to the end of oncological treatment.

Discussion and conclusion
Renal transplantation is considered the optimal treatment for children and adolescents with ESKD [6-12]. In the study published in 2004, Stephen P. McDonald et al. observed that patients who have to wait longer for renal transplantation have worse overall outcomes, because of the prolonged exposure to side effects related to hemodialysis such as cardiac problems and infections [6]. Other authors showed that transplant survival is negatively influenced by the duration of dialysis before transplantation, even considering bias about the choise of patients for preemptive transplant [14]. For this reason, the authors recommend to increase the rates of transplantation among children with

ESKD and suggest to placed on the national transplant list within six months of their anticipated dialysis start date [6, 8, 13, 14].

The placement on the waiting list for renal transplantation of patients with pre-existing malignancies, however, is often postponed because of the fear of cancer recurrence and/or of the effects of post-transplant immune suppression, which is often incriminated as the cause of reactivation and worsening of the malignant disease [10].

The optimal waiting time for transplantation is an open issue in oncologic children with ESKD due to WT and/or its treatment. Different international guidelines recommend 2 years waiting time after the end of oncologic treatment before renal transplantation [7, 8]. However, other authors suggest that, for oncologic patients, pre-transplant waiting time should be individualized, based on the patient's characteristics (age, general health conditions) and tumor features (type, stage, and grade) [9]. The study published by Grigoriev et al in 2012 and based on data of the National Wilms Tumor Study (NWTS) showed that the outcome after renal transplantation of patients previously treated for WT was not worse than that of other patients of the same age and sex transplanted for other causes, both in terms of mortality and of organ rejection [9]. For this reason, some authors proposed to re-evaluate the 2 years waiting time to renal transplantation for patients treated for WT [10, 11].

Our 2 cases reported developed ESKD after late relapse of WT, requiring bilateral nephrectomy to achieve CR. There is no consensus on the timing of transplantation in these cases. On the one hand, it is risky to transplant too early a patient with cancer history, while on the other hand both physical and psychological late effects of prolonged hemodialysis are well known. Thus, in our opinion, waiting time before renal transplantation should be based on the single patient's history and tumor characteristics (type, stage, histology, response to treatment) to evaluate possibility of event free and overall survival, and, whenever possible, it should be reduced from the standard 2 years, even in view of the most recent epidemiological data, the development of more effective and personalized oncologic treatments and the improvement of immunosuppressive therapies following transplantation [10].

In the first case we described, the patient was in CR at the last 5 years' follow-up from the end of oncologic treatment. She developed cardiac problems related both to tumor treatment and mostly to hemodialysis. Considering the patient's age and the long follow-up characterized by persistent CR, the patient was put on the waiting list for renal transplantation. It remains doubtful whether this patient should be placed early on the waiting list for renal transplantation. The patient died of complications related to infection (Sars-Covid-19) before having the possibility to undergo transplantation.

In the second case we described, the patient was in CR of the disease at the last 20 months' follow-up from the end of treatment. She was 22 years old (very late recurrence of WT, at first diagnosis she was 4 years old), presented a low-grade heart disease, and she wished for a better quality of life. On the basis of our previous experience (case 1) and of several reported studies [5, 7, 9, 12], the patient was put on the national waiting list for renal transplantation in agreement with the nephrology team, even considering the psychological status of the patient and her wish to have a better life. Patient perspective in this case is high about health and quality of life.

In conclusion, to the best of our knowledge, there are few reported studies on patients that experience ESKD after late relapse of renal tumor. Relapse of WT is rare and late relapse is even rarer [2; 4; 5]. These observations, together with the need to reduce the side effects of long term hemodialysis, that are both physical (e.g. cardiologic, growth, infectious complications) and psychological, would suggest to accelerate the placement of these patients on the waiting list for transplantation.

In our cases the different time to propose renal transplantation was associated to different outcome. Clinicians should have common lines about the time of renal transplantation in pediatric oncology, however a personalized planning could be suggested after multidisciplinary discussion, evaluating case to case. Among Italian specialists in kidney tumor, the most recent approach is based on individual patient and tumor history, presence of CR, surgical history, co-morbidities and current health state of the child. The presented field needs more knowledge to improve the clinicians,

further larger case series are necessary to evaluate outcome related timing of renal transplant, threrefore we suggest active collaboration and sharing results between oncology centers.

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STATEMENT OF ETHICS
Ethical approval of the ethics committee of the Institute G. Gaslini:
This retrospective review of patient data did not require ethical approval in accordance with local/ national guidelines

CONFLICT OF INTEREST STATEMENT
"The authors have no conflicts of interest to declare"

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No fund was necessary for this study
No sponsor had involvement in: the study design the collection, analysis and interpretation of data the writing of the report the decision to submit the paper for publication

AUTHOR CONTRIBUTIONS
B.T., C. P. and A.L conceptualized and drafted the manuscript.; M. M., S.S, and M. A. were involved in the clinical care of the patients; S. F processed the radiological features; C.B and V. V conducetd the histological analysis; Z.S was involved in the registration of parental consent; G.A was involved in the critically review. All the authors approved the final version and the submission.

DATA AVAILABILITY STATEMENT
The data that support this study and the patient consent are available in the patient's medical record and in the Italian pediatric tumor registry of the Italian Association of Pediatric Hematology and Oncology (AIEOP).
Further enquiries can be directed to the corresponding author.

WRITTEN INFORMED CONSENT FOR PUBLICATION OF CASE
Case1: Written informed consent was obtained from the parent of the patient for publication of the details of their medical case and any accompanying images.
Case2: Written informed consent was obtained from the parent of the patient for publication of the details of their medical case and any accompanying images.

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material.

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Figure Legends

Fig. 1. Volumetric CT post CM. Coronal plane. A voluminous heterogeneous mass within the right renal space. The right kidney is not visualized. legend d text.

Fig. 2. Volumetric CT post CM. Axial plane; thoracic outel metastasis; solid heterogeneous lesion with CE at the thoracic outlet in the left- median site, trachea is dislocated and compressed.

Fig. 3. Volumetric CT post CM. Axial plane. A voluminous and heterogeneous mass originating from the left kidney, which is compressed and displaced medially