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OPENING AN ONCONEPHROLOGY CLINIC: RECOMMENDATIONS AND BASIC REQUIREMENTS

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Keyword list:	oncology, Cancer, chronic renal insufficiency, outpatient clinic, multidisciplinary team

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3 **OPENING AN ONCONEPHROLOGY CLINIC: RECOMMENDATIONS AND BASIC**
4 **REQUIREMENTS**
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Abstract

Onconeurology is a rapidly evolving subspecialty that covers all areas of renal involvement in cancer patients. The complexity of the field may benefit of a well-defined multidisciplinary management administered by a dedicated team. Since there is an increasing need to address the needs of this population in dedicated outpatient clinics, it is critical to highlight basic characteristics and to suggest areas of development. In this brief perspective article we analyze the requirements of an Onconeurology clinic in terms of logistic, critical mass of patients, and building of a multidisciplinary team. We will further discuss about which patients to refer and which conditions to treat. The last part of the paper is dedicated to education and performance indicators and to analyze the potential advantages of applying the hub and spoke model to this field. The ultimate aim of this experience-based manuscript is to initiate to debate about how an Onconeurology outpatient clinic might look like in order to ensure the highest quality of care to this growing population of patients.

KEY WORDS: onconeurology; cancer; kidney; outpatient clinic; multidisciplinary team.

RUNNING TITLE: onconeurology outpatient clinic.

Introduction: the cancer-kidney connection

Onconeurology is a rapidly evolving subspecialty area that focuses on all aspects of kidney disease in cancer patients. Recently, we proposed a “decatalogue of onconeurology” to highlight several of the areas where nephrologists and oncologists should collaborate to provide cutting-edge care for patients afflicted with cancer and kidney diseases¹. In that paper, we highlighted the following 10 points of contact between the two specialties 1) acute kidney injury (AKI) and chronic kidney disease (CKD) in cancer patients; 2) nephrotoxic effects of anticancer therapy; 3) paraneoplastic renal manifestations; 4) management of patients nephrectomized for a kidney cancer; 5) renal replacement therapy and oncological treatments; 6) kidney transplantation in cancer survivors and cancer risk in ESRD patients; 7) oncological treatment in kidney transplant patients; 8) pain management in cancer patients with concomitant kidney diseases, 9) development of guidelines specific for onco-nephrology patients and 10) design of clinical trials with onco-nephrology endpoints¹.

Well-defined multidisciplinary management of cancer patients with kidney disease can help ensure the highest quality of care that is administered by a dedicated specialty team with experience in these complex issues.

To aid implementation of this model, it is critical to identify recommendations and minimal requirements for the development of onconeurology outpatient clinics. There are examples of these types of multidisciplinary clinics in other fields of oncology where various specialists are brought together to improve outcomes and care pathways^{2,3}. The objective of our experience-based paper is to initiate a dialogue on what such a clinic might look like to successfully serve this growing population of patients.

Onconeurology clinics – Basic requirements

To develop and sustain a successful outpatient clinic for patients suffering from cancer and kidney disease, a number of basic requirements must be met. In our opinion, the following requirements are needed to create a successful and efficient onconeurology outpatient clinic.

1) Critical mass of patients

For many reasons, there should be a sufficient number of patients enrolled in the clinic. This is to ensure operational efficiency, financial viability and to develop expertise in the unique overlap of kidney problems seen in patients with cancer. Recent studies demonstrated that the prevalence of estimated glomerular filtration rate (eGFR) below 60 ml/min in patients affected by solid tumors overall exceed 12%⁴ and a 1 year risk of AKI of any stage may be as high as 17% for incident cancer patients⁵. Since the cancer incidence in Europe and USA approaches 300 cases per 100,000 inhabitants/year⁶, the clinic should be affiliated with a large or medium-size hospital (serving at least 500,000 inhabitants). At least 150 new patients per year would be thus considered a sufficient size to maintain a robust clinic. In certain major cancer centers it is ideal that the onconeurology clinic is physically housed in the cancer hospital. The choice of 150 new patients, as a minimum number of cases justifying the development of an Onco-Nephrology clinic, is empiric, though justified on the basis of the experience of three of the co-Authors of this paper, who have already created such clinics across Europe; of course, this should be considered just as a starting number, which is expected to increase over time.

In most academic centers, creating this critical mass will be needed to enhance the experience and expertise of the onconeurologist.

2) Proximity to the Hematology and Oncology ward

In addition to an adequate patient number, the clinic should be located within a reasonable distance from the primary site of oncology care. This is particularly important when a patient develops significant AKI or progressive CKD that might impede active cancer therapy. Rapid nephrology evaluation and treatment would be greatly facilitated by a nearby onconeurology clinic.

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3 Furthermore, an active, local and bidirectional relationship between nephrologists
4 and oncologists would promote shared decision-making and development of
5 collaborative care models. This would engender a comprehensive evaluation of
6 patients that would hopefully result in improved outcomes⁷. For example, the
7 onconephrology team could provide critical information about life expectancy and
8 quality of life for patients facing decisions regarding dialysis initiation. This
9 integrative, patient-centered, medical approach is key to ensure appropriate and
10 optimized care of the patient and their diseases, including cancer and comorbidities.
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15 An ideal model is to allow the onconephrologist to see the cancer patient in
16 the hematology/oncology office. This might be logistically possible in some centers
17 and not others. Thus, a reasonable physical proximity would be a key requirement to
18 provide a structured and multidisciplinary environment for effective management of
19 patients referred to the clinic.
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24 Of course, not every given patient has to be physically seen by the
25 multidisciplinary group; furthermore, a tele-medicine approach could be very useful
26 within the hub and spoke model described later within this manuscript.
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32 *3) Availability of Medical Records across Clinics*

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34 The history of patients with cancer is complicated with multiple visits to
35 various specialists and complex medical regimens that can change rapidly depending
36 upon side effects and tumor response. This is particularly true for patients with
37 extended therapeutic courses. These patients have often undergone a large number
38 of diagnostic studies and treatment regimens. The availability of original source
39 documents (which, once again, is facilitated by proximity) would thus be key to
40 having a complete understanding of the patient's past and present medical (and
41 oncologic) history. The easy availability of this information would facilitate a rapid,
42 comprehensive evaluation by the consulting nephrologist.
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51 *4) Shared (electronic) database*

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53 Since the subspecialty of onconephrology is still in its infancy, both cancer
54 specialists and nephrologists may benefit immensely from knowledge of previous
55 cases, their treatments and outcomes. A comprehensive data-base containing
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3 electronic medical records (EMRs) would represent a source of precious information
4 (both prospective and retrospective) for clinical and research purposes. Such
5 databases can be “mined” to look for outcomes of specific subgroups of patients and
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7 can be used to develop hypotheses for future studies.
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10 11 *5) Referral to the Onconeurologist*

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13 Although an onconeurology outpatient clinic may operate once or twice a
14 week (or more frequently as needed), a dedicated onconeurologist should always
15 be available to provide expertise.
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18 Since a sizeable number of patients falling within the competence of an
19 onconeurological evaluation are often hospitalized, an onco-neurology
20 consultation should be available, on demand, also for inpatients; specific protocols
21 should thus be implemented within the hospital in order to clearly define when this
22 kind of consultation is needed within the inpatient ward (e.g. in the case of those
23 conditions reported in table I), and how to ask for it.
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28 The onco-neurology consultant must be versed and knowledgeable of the
29 complex relationships between cancer and the kidney, the pharmacological
30 properties of all antineoplastic drugs, and the harm to benefit ratio of antineoplastic
31 treatment strategies in patients with underlying kidney disease.
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35 Considering the need of evaluating some of these patients on a short notice,
36 as well as obvious organization issues such as vacations, illnesses, etc ..., more than
37 one dedicated specialist is needed in order to fulfill all the above requirements.
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40 Overall, a curriculum in onconeurology, such as the one developed by the
41 American Society of Nephrology⁸, would be useful to facilitate competency in this
42 complicated area.
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46 47 *6) Multidisciplinary Team*

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49 A multidisciplinary approach is critical for the success of this model⁹.
50 Multidisciplinary care requires a pro-active and bidirectional relationship between
51 the various specialists (see core team below) involved in the patient’s care.
52 Furthermore, performance indicators and regular assessment of outcomes are
53 essential to monitor the effectiveness of the outpatient clinic and to allow changes
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3 and improvements over time. It is important to recognize that multidisciplinary care
4 does not mandate the participation of onconeurologists on all tumor boards. We do
5 believe that a significant number of those patients brought for multidisciplinary
6 discussion into the GU tumor board could benefit from the presence of a
7 nephrologist. In addition, the onconeurologist's opinion can be sought when
8 needed for complex cases where kidney disease is integral to the diagnostic or
9 therapeutic plans. Where clear renal issues exist or may develop, protocols for early
10 nephrology involvement are important. In complex drug toxicities such as immune
11 check-point inhibitor induced acute nephritis¹⁰ or venetoclax induced tumor lysis
12 syndrome¹¹, an onconeurologist's expertise can help standardize care in the
13 inpatient and outpatient settings.
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23 *7) Core team*

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25 A core team of various specialists dealing with cancer patients with kidney
26 disease and issues is mandatory. The core team would consist of nephrologists,
27 hematologists and oncologists along with a dedicated data manager, nursing and
28 care coordinator team members. The team members should ideally have a
29 specialized training in onconeurology and, should spend an agreed amount of
30 weekly time with these patients to maintain proficiency⁸. Participating nephrologists
31 should also partake of continuing professional medical education. All core team
32 members must attend multidisciplinary meetings for case management and audit
33 purposes. Other specialists including urologists, radiation therapists, pathologists,
34 radiologists, palliative care-providers, and others would be invited to attend
35 multidisciplinary rounds, as needed. This model currently exists in many U.S. Cancer
36 Centers and emerges in many European countries. *Notably, within the Onco-
37 Nephrological web community of the American Society of Nephrology, this is a topic
38 that has been recently the object of a dedicated forum ([http://community.asn-
39 online.org/communities/community-home?communitykey=0ca61c6c-1f2f-4f15-
40 9ae5-86fc6ef4c260&tab=groupdetails](http://community.asn-online.org/communities/community-home?communitykey=0ca61c6c-1f2f-4f15-9ae5-86fc6ef4c260&tab=groupdetails), accessed on May 8, 2018).*
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52 In addition, case discussions, which should be held at least weekly, must be attended
53 by all involved professionals.
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3 Furthermore, the role of a dedicated Pharmacologist, within or not the core
4 team, is in our opinion critical in order to provide advice on possible pharmacologic
5 interactions (in a population of patients highly comorbid and thus taking many
6 different drugs), and to explore pharmacokinetic properties of each given
7 oncological drugs in CKD patients, as well as in those on dialysis.
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11 12 13 *8) Involvement of other health Professionals*

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15 Depending on different organization systems, which can greatly vary from
16 country to country, different health professionals, including physician extenders,
17 nurses, and post-graduate students, could be involved in the activities of the clinic,
18 especially when patients need to be seen on a short notice or for frequent follow-up
19 controls.
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24 25 *9) Availability of certain diagnostic tests*

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27 Ideally, a histological evaluation of both non-neoplastic and neoplastic tissue within
28 the pathologic specimens of resected kidney cancer patients would be mandatory, as
29 claimed by the 2012 International Society of Urologic Pathology (ISUP) consensus
30 conference¹². This evaluation would indeed provide important details for the future
31 management of these patients. However, since the implementation of this
32 evaluation could be troublesome on a wide scale, we believe that optical microscopy
33 analysis of the normal tissue should be reported in almost all patients' pathological
34 reports, while immunofluorescence and/or electron microscopy should be
35 performed in more specialized centers (i.e. the hubs, as reported below) whenever
36 needed, and tissue preserved for possible future analyses.
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44 Following the 2012 International Society of Urologic Pathology (ISUP) consensus
45 conference¹², has become mandatory; indeed, the study of the non-neoplastic tissue
46 could provide informations of the utmost utility for a comprehensive nephro-
47 oncological evaluation.
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51 Furthermore, a comprehensive and efficient workup for a patient attending the
52 Onco-Nephrology clinic often requires the prompt execution of few diagnostic tests.
53 Those providing important informations for many patients include renal ultrasound
54 (including Doppler interrogation), venous blood gas (VBG) analysis, and ambulatory
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3 blood pressure monitoring (ABPM), though the importance of the availability of the
4 latter two has not been agreed upon by all co-Authors. Indeed, although
5 hypertension is, by far, the most common treatment-related renal adverse event
6 observed in cancer patients on antiangiogenic treatment, it is clear that ABPM is not
7 strictly necessary in many other cancer patients. As far as VBG, although it provides
8 in timely manner important informations, able to immediately drive therapeutic
9 interventions, such as pH, bicarbonates, ionized calcium, and potassium levels, these
10 informations can be also provided without the need of a blood gas and in a timely
11 manner by a stat lab. Thus, since in some Countries (e.g. the US) institution-specific
12 regulations don' t allow the presence of lab equipment in outpatient clinical space,
13 stat labs should be regarded as a realistic substitute for VBG.
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23 These tests, in particular renal ultrasound, maintain the potential to provide critical
24 information about the cause of AKI or CKD in the cancer patient, monitor for acid-
25 base disturbances, a blood pressure changes due to anti-cancer drugs (both
26 hypotension and hypertension). The ability to promptly perform these tests would
27 allow rapid, efficient care in the spirit of the state-of-the-art Onco-Nephrology clinic
28 care plan.
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35 **Which patients are appropriate for the Onco-Nephrology clinic?**

36 In some countries, chemotherapy is only validated after regular multidisciplinary
37 meetings. At that stage, it might be interesting to obtain a minimal renal check-up
38 before any treatment to identify "at risk patients" and further educate oncologists
39 and patients about a number of classical kidney failure risks.
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44 In previous publications, we and others have identified the main areas of interest
45 and intervention of Onco-Nephrology^{1,13-15}. In our opinion, there are categories of
46 cancer patients who must be always referred to the Onco-Nephrology outpatient
47 clinic for a comprehensive evaluation. Table 1 notes the types of patients and
48 reasons for referral to the outpatient clinic.
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54 **Minimal workup for the Onco-Nephrology patient**

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3 The minimal workup needed by a cancer patient with some form of kidney
4 disease is summarized in table 2. In general, the workup should include routine
5 generic examinations and tests, as well as tests specific for the kidney or oncological
6 aspects of the patient's care.
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10 It is critical that patients have an accurate estimate of GFR to ensure problem
11 dosing of medications and avoidance of side effects. The best estimating equation
12 for GFR to gauge kidney function has not been well studied in patients with cancer
13 and kidney disease. These tests have their strengths and limitations in the general
14 population and likely have other issues in the patients being evaluated in the
15 onconephrology clinic¹⁶⁻¹⁹. Although some authors have suggested that MDRD could
16 underestimate kidney function in cancer patients^{20,21}, the MDRD and CKD-EPI
17 equations are still the two equation recommended also in this setting²²⁻²⁴. It is likely
18 that they will provide similar estimates of kidney function in patients with stable CKD
19 and they are not appropriate to use in patients with AKI where patient's GFR is not in
20 the steady state²⁵. A recent publication evaluating GFR estimating equations in
21 cancer patients noted that BSA-adjusted CKD-EPI method appears to be the most
22 accurate published model to estimate GFR in patients with cancer. BSA-adjusted
23 CKD-EPI, based on the analysis of data from 2,582 cancer patients using 51Cr-EDTA
24 GFR measurement as the gold standard, was found to be the most accurate and least
25 biased published model to estimate GFR¹⁷. The authors also developed a new model
26 that further improves the estimation of GFR and allows calculation of predictive
27 confidence intervals for this estimation. The new model has been implemented as an
28 online tool found at the following link:
29 <http://tavarelab.cruk.cam.ac.uk/JanowitzWilliamsGFR/>. This new model to estimate
30 GFR may represent a new standard of care and should be further examined along
31 with BSA-adjusted CKD-EPI in clinical onconephrology practice.
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49 **Diseases managed in the Onconephrology outpatient clinic**

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51 Based on our experience, the areas where a joint onconephrology approach
52 (consultation) is mandatory are those reported in table 3¹⁴. The involvement of
53 specialists other than nephrologists and oncologists should be considered in many of
54 the case discussions, diagnostic approaches, and treatment plans.
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Development of protocols for the Onconeurology clinic

The development of specific protocols for the screening, management, and follow-up of cancer patients with various kidney problems would be one of the major goals of onconeurology clinic. Different protocols should be proposed and discussed within the core team, brought to the attention of multidisciplinary teams (MDTs), and then disseminated to all onconeurology clinics (table 4). These protocols should be shared across centers in order to support development of best practices.

In addition to developing various clinical protocols, it should be part of the onconeurology core team's mission to participate in the proposal, design, and conduction of clinical trials addressing specific issues related to cancer and kidney disease. Finally, lobbying to introduce well-defined and clinically relevant nephrology endpoints into oncological clinical trials (from phase I to post-marketing phase IV studies) would be of the utmost importance²⁶

Audits and (proposed) indicators of performance

The onconeurology clinic must hold regular internal audit meetings in order to review indicators of performance, establish or change procedures, and amend protocols as necessary^{2,27}. Written protocols should be developed and agreed upon by the multidisciplinary members, and then discussed and re-evaluated at any audit. Revising many of the proposed indicators of performance over time, in order to dismiss those not relevant, and implement novel ones (e.g. those emerging from the use of novel anticancer agents/strategies), will be an integral part of the indicators/audits system we propose.

Ideally, among possible initial indicators of performance, we propose those described in table 5.

The "hub and spoke" model for onconeurology

While one of the requirements for an onconeurology outpatient clinic is the presence of a critical mass of patients, the need for an onconeurology consultation can also occur in a small, peripheral hospital. We believe that the concept of the hub

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3 and spoke model^{28,29} could optimally be applied to onconeurology. Indeed, the goal
4 of the hub and spoke model is to position a specialized care delivery facility as a
5 central hub, and build a network of feeders or spoke facilities. This system creates
6 value by generating learning curve benefits at the hub, as well as by operating all
7 assets within the network at maximum utilization. Since one of the goals of this
8 model is to bring complex cases to the central hub, where they could be managed at
9 the highest level of competence, this could be achieved either at the central hub or
10 virtually. Web based consultations, or even MDT rounds could potentially replace
11 physical visits in the case of logistical issues, bringing the competence of the hub
12 directly to the spoke.
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22 **Education and training to create the Onco-Nephrologist**

23 In the introduction to the ASN core curriculum in onconeurology⁸, Perazella
24 and Rosner clearly stated that one of the goals of such a tool was to “... *provide the*
25 *ASN membership, including veteran nephrologists, newly minted nephro-clinicians,*
26 *and fellowship trainees, with the building blocks on which further information can be*
27 *added as technology advances*”. This would be a potential model to follow on an
28 international level around the world. Nephrologists must be prepared to care for
29 patients with cancer and renal complications. Indeed, as already evidenced, the
30 renal manifestations of cancer have many unique features, and these conditions
31 often require specialized approaches to manage all of them. Furthermore, the
32 rapidly evolving field of cancer treatments requires a comprehensive approach from
33 the different and varied expertise of nephrologists, oncologists, and many other
34 specialists. As such, it is essential for all who are interested in onconeurology to
35 develop expertise in the practice of this intriguing and complex subspecialty. Specific
36 courses in post-graduate training in Nephrology and Oncology could be employed to
37 increase the awareness of onconeurology issues, and to prepare the next
38 generation of specialists in this subspecialty.
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53 **Foreseen obstacles in the development of an onconeurology outpatient clinic**

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3 The development and implementation of every novel activity is almost
4 always coupled with difficulties, obstacles, and barriers; this is for sure also the case
5 of our proposal.
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8 Recognizing these pitfalls is the first step to overcome them. According to our
9 experience, we have summarized these foreseen obstacles in Table 6, coupling each
10 requirement we have highlighted with relative obstacles. Notably enough, in our
11 opinion, the first and most important obstacle to overcome is the typical nihilistic
12 approach surrounding patients with both kidney diseases and cancer.
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Conclusions

Due to the dramatic improvements in cancer treatment, a growing number of patients affected by cancer now survive longer, often with a adequate quality of life. However, the presence of concomitant chronic illnesses, including kidney disease, may greatly complicate their care and alter their quality and quantity of life. The relationship between kidney disease and cancer could be regarded as 'circular'³⁰. For example, the presence of a tumor or its treatment may directly or indirectly damage renal function and the presence of kidney disease in cancer patients may worsen prognosis, increase mortality, and disturb the bioavailability and/or safety profile of antineoplastic drugs in patients with underlying kidney disease.

Onconephrology is presently more experience-, than evidence-based. Indeed, onconephrology has developed in recent years with the main intent of managing those orphan patients (e.g. those with CKD, ESRD, on dialysis, transplanted, etc ...) who are not enrolled into clinical trials (the cornerstones of evidence-based medicine), who cannot benefit from the availability of guidelines (which indeed do not exist), or even of sound supporting literature (mainly limited to single case reports or small retrospective series). Only a thorough knowledge of the issues of onconephrology and of the drugs and their pharmacokinetic properties in patients with cancer and kidney diseases, together with a tight inter-specialty collaboration, can provide these patients a better treatment and management.

Thus, a multidisciplinary onconephrology team, led by cancer specialists and nephrologists, but also including other health professionals, is critical to providing the best possible care for this group of cancer patients. Here we have proposed minimal requirements and recommendations to develop an onconephrology outpatient clinic, with the overall aim of providing experience-based considerations that will initiate further discussion on this important and growing specialty area. Finally, as far as multidisciplinary, we cannot but agree with the following strong statement by Champiat et al.: *"Organ specialist ... referral is needed for mainly two reasons: for oncologists to learn proper management of specific ... toxicities, but also for organ specialists to increase their knowledge about these new drug-mediated toxicities and therefore creating a virtuous circle for patients management"*³¹.

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Table 1. Patients for whom referral to the onconeurology Clinic is suggested

<i>Type of patient(s)</i>	<i>Main issue(s)</i>
Cancer patients with kidney impairment before, during and after active cancer treatment	<ul style="list-style-type: none"> - To guarantee the best cancer treatment possible, without unnecessary dose reduction and/or treatment interruptions, which could hamper the possibility of success of the oncological treatment
Cancer patients at risk of kidney impairment <ul style="list-style-type: none"> - due to concomitant illnesses (e.g. hypertension, diabetes, etc.) - due to the potential nephrotoxicity of the planned treatment 	<ul style="list-style-type: none"> - To prevent the development of kidney impairment, possibly leading to dose reduction or treatment interruption - education of oncologists and patients about classical kidney failure risks
Cancer patients developing adverse renal events from antineoplastic treatment	<ul style="list-style-type: none"> - AKI - Worsening of CKD - Hypertension - Proteinuria - Electrolyte disturbances - TMA
Cancer patients at significant risk of Contrast-Induced-Nephropathy	<ul style="list-style-type: none"> - Prevention of AKI or of worsening of CKD through implementation of prophylactic measures
Kidney cancer patients at risk for post-surgical (or post-ablative) AKI or progressive CKD	<ul style="list-style-type: none"> - Prevention of AKI or of worsening of CKD - Management of treatment-related AEs
Patients with urothelial cancer (all)	<ul style="list-style-type: none"> - Prevention of AKI or of worsening of CKD - Prevention/management of obstructions - Prevention/management of chronic infections - Management of treatment-related AEs
Patients with suspected or de facto paraneoplastic glomerulopathies	<ul style="list-style-type: none"> - Screening for an occult cancer (if any) - Diagnosis - Management strategies (e.g. use of immune-suppressive agents in the cancer patient)
Transplantation patients <ul style="list-style-type: none"> - donors - recipients - transplanted patient who develops cancer 	<ul style="list-style-type: none"> - When to allow transplantation or donation in a patient with previous or an active cancer - Management strategies (e.g. use of immune-suppressive agents in the cancer patient)
Cancer patients on dialysis	<ul style="list-style-type: none"> - Management of drug dosing, toxicity - Use of erythropoietin stimulating agents - Shared decision making
Hematological cancer patients	<ul style="list-style-type: none"> - Management of renal involvement in myeloma and lymphomas - Management of secondary amyloidosis

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Bone metastases in cancer patients with CKD	<ul style="list-style-type: none">- Management of bone-targeted therapies (bisphosphonates or denosumab)- Management of bone-targeted therapies-induced hypocalcemia
AKI, acute kidney injury; CKD, chronic kidney disease; TMA, thrombotic microangiopathy; CIN, contrast induced nephropathy; AEs, adverse events	

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Table 2. Clinical evaluation of the patient with cancer and kidney disease

<ul style="list-style-type: none"> • Physical examination
<ul style="list-style-type: none"> • Evaluation of co-morbidities and pre-existing kidney impairment (clinical and subclinical)
<ul style="list-style-type: none"> • Evaluation of ongoing (and previous) therapies, both oncological and not oncological
<ul style="list-style-type: none"> • Renal function tests <ul style="list-style-type: none"> - Estimated glomerular filtration rate (eGFR) with a CKD-EPI formula - When needed, directly measure eGFR (creatinine clearance, nuclear medicine GFR evaluation, etc ...)
<ul style="list-style-type: none"> • Basic hematology, including differential white blood cell count
<ul style="list-style-type: none"> • Urinalysis and examination of urinary sediment examination; quantification of proteinuria
<ul style="list-style-type: none"> • Electrolytes and serum enzymes (including serum calcium, phosphorus, uric acid and magnesium, LDH and uric acid). Obtain trends of all pertinent labs including SCr, LDH, CBC and urine protein/creatinine ratio
<ul style="list-style-type: none"> • Acid-base balance and abnormalities
<ul style="list-style-type: none"> • Blood pressure (including ABPM whenever necessary)
<ul style="list-style-type: none"> • Basic imaging: renal/abdominal US
<ul style="list-style-type: none"> • Basic imaging: oncological disease status evaluation, as appropriate (CT, MRI, etc ...)
<p>CKD-EPI, chronic kidney disease epidemiology; CBC, complete blood count; SCr, serum creatinine; LDH, lactate dehydrogenase; ABPM, ambulatory blood pressure monitoring; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging.</p>

Table 3. Disease management in the Onconephrology clinic

<ul style="list-style-type: none"> • Management of renal AEs from anticancer therapy and dose modification for <ul style="list-style-type: none"> - cytotoxic chemotherapy, - targeted agents, - immune checkpoint inhibitors and - bone targeting agents, in patients with conserved or altered renal function (including ESRD and dialysis patients)
<ul style="list-style-type: none"> • Management of renal complications from <ul style="list-style-type: none"> - surgery - radiation therapy - other diagnostic and therapeutic procedures (e.g. renal stenting, etc.)
<ul style="list-style-type: none"> • Management of CIN
<ul style="list-style-type: none"> • Management of transplantation patients' issues <ul style="list-style-type: none"> - management of kidney transplant patient that develops a cancer - clearance (or not) of a cancer patient to donate for kidney transplantation - clearance (or not) of a cancer patient to receive a kidney transplantation - administration of targeted therapy and or immunotherapy in a kidney transplant patient.
<ul style="list-style-type: none"> • Management of paraneoplastic nephrological syndromes, including screening or not these patients
<ul style="list-style-type: none"> • Choice of anti-pain therapy and dose adaptation in cancer patients with renal impairment
<ul style="list-style-type: none"> • Discussion of ethical issues (to treat or not to treat cancer patients in dialysis or with ESRD)
<p>AEs, adverse events; ESRD, end stage renal disease; CIN, contrast induced nephropathy</p>

Table 4. Onco-Nephrology protocols

• Screening and follow-up protocols to prevent kidney damage for each given antineoplastic agent
• Screening and follow-up protocols to prevent kidney damage from radiology contrast-media
• Developing indications for kidney biopsy, and implementing its use in cancer patients
• Screening and follow-up protocols for cancer patients in dialysis and with ESRD
• Screening and follow-up protocols for transplantation patients (evaluation and possibly prevention of the risk of malignancy)
• Screening and follow-up protocols for transplantation candidates <ul style="list-style-type: none">- if and when to transplant a patient who previously had cancer,- if and when allowing the donation from a patient who previously had a cancer

Table 5. Performance indicators for an Onco-Nephrology clinic

<i>Indicator of performance</i>	<i>Reason(s)</i>	<i>Value to be achieved (on 1st year)</i>
Percentage of patients discussed by the core team	To ensure that (ideally) all patients presenting with Onco-Nephrology issues are adequately evaluated at least by the core team	100%
Percentage of patients brought to the attention of the MDT	To ensure that all complex patients presenting are brought to the attention of and discussed within each given MDT	100%
Number of episodes of AKI from anticancer treatment	AKI episodes leads to worsening of cancer patients' prognosis (especially in terms of reduced OS); furthermore, increases also CKD	Reduction of at least 25% as compared to the previous year
Number of episodes of CIN	CIN episodes lead to both AKI and worsening of CKD	Reduction of at least 25% as compared to the previous year
Number of visits to ER ward due to kidney toxicity from oncological treatments	Increase of costs and hospitalization rates	Reduction of at least 25% as compared to the previous year
Number of hospital admissions due to kidney toxicity	Increase of costs	Reduction of at least 25% as compared to the previous year
Number of treatment interruptions due to kidney toxicity	Potentially hampers treatment efficacy	Reduction of at least 25% as compared to the previous year
Number of treatment withdrawals due to kidney toxicity	Hampers treatment efficacy precluding the continuation of potentially life-extending treatments	Reduction of at least 20% as compared to the previous year
Number of drug-related adverse reactions due to kidney disease	Increase morbidity and (potentially) also mortality, as well as hospitalization rates; increase also treatment interruptions and withdrawals	Reduction of at least 25% as compared to the previous year
Patients' satisfaction	Linked to improved QoL	100%
Healthcare workers' satisfaction	Linked to improved medical service quality and patients' satisfaction.	100%
MDT, multidisciplinary team; CKD, chronic kidney disease; CIN, contrast induced nephropathy, QoL, quality of life		

Table 6. Foreseen obstacles in establishing an outpatient onconeurology clinic

<i>Specific requirement</i>	<i>Obstacle(s)</i>
Critical mass of patients	<ul style="list-style-type: none"> - Presence of a small oncology/hematology service - Nihilistic approach to patients with both kidney diseases and cancer
Proximity to the hematology/oncology ward	Structural difficulties (especially in Hospitals not built to favour multidisciplinary)
Availability of medical records across clinics	Not an issue
Shared (electronic) data-base	Not an issue
Referral to the Onco-Nephrologist	<ul style="list-style-type: none"> - Clear-cut identification of the Onco-Nephrology referral specialist within the hospital - Clear-cut definition of the patients to refer for consultation - Information/education of physicians who should know when an onconeurological referral is needed
Multidisciplinary team and core team	<ul style="list-style-type: none"> - Time - Bringing together and motivating different specialists towards a real multidisciplinary consultation - Nihilistic approach to patients with both kidney diseases and cancer - Need for a specific training and for maintaining proficiency in Onco-Nephrology
Involvement of other health professionals	Bringing together and motivating different health professionals and caregivers
Availability of certain diagnostic tests	Not an issue
Appropriateness of patients	<ul style="list-style-type: none"> - Clear-cut definition of the patients to refer for consultation - Nihilistic approach to patients with both kidney diseases and cancer
Minimal workup	<ul style="list-style-type: none"> - Sharing minimal requirements among different specialists - Sharing a common language - Clear-cut evaluation of kidney function
Disease management	Nihilistic approach to patients with both kidney diseases and cancer
Development of specific protocols	Identification of topics and objectives
Audits and indicators of performance	<ul style="list-style-type: none"> - Time and personnel - Variability of indicators over time
Hub and spoke model	<ul style="list-style-type: none"> - Costs - Bringing together and motivating different structures and health

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	professionals
Education and training	<ul style="list-style-type: none">- Identification of educational needs- Standardization of trainees' curriculum

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