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Guidelines for the definition of time-to-event end points in renal cell cancer clinical trials: results of the DATECAN project†

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Background: In clinical trials, the use of intermediate time-to-event end points (TEEs) is increasingly common, yet their choice and definitions are not standardized. This limits the usefulness for comparing treatment effects between studies. The aim of the DATECAN Kidney project is to clarify and recommend definitions of TEE in renal cell cancer (RCC) through a formal consensus method for end point definitions.

Materials and methods: A formal modified Delphi method was used for establishing consensus. From a 2006–2009 literature review, the Steering Committee (SC) selected 9 TEE and 15 events in the nonmetastatic (NM) and metastatic/advanced (MA) RCC disease settings. Events were scored on the range of 1 (totally disagree to include) to 9 (totally agree to include) in the definition of each end point. Rating Committee (RC) experts were contacted for the scoring rounds. From these results, final recommendations were established for selecting pertinent end points and the associated events.

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Results: Thirty-four experts scored 121 events for 9 end points. Consensus was reached for 31%, 43% and 85% events during the first, second and third rounds, respectively. The expert recommend the use of three and two endpoints in NM and MA setting, respectively. In the NM setting: disease-free survival (contralateral RCC, appearance of metastases, local or regional recurrence, death from RCC or protocol treatment), metastasis-free survival (appearance of metastases, regional recurrence, death from RCC); and local–regional-free survival (local or regional recurrence, death from RCC). In the MA setting: kidney cancer-specific survival (death from RCC or protocol treatment) and progression-free survival (death from RCC, local, regional, or metastatic progression).

Conclusions: The consensus method revealed that intermediate end points have not been well defined, because all of the selected end points had at least one event definition for which no consensus was obtained. These clarified definitions of TEE should become standard practice in all RCC clinical trials, thus facilitating reporting and increasing precision in between trial comparisons.

Key words: clinical trials, DATECAN, recommendations, renal cell cancer, time-to-event end points

introduction

Many different time-to-event end points (TEEs) are used in evaluating treatment in cancer clinical trials in general and for trials of patients with renal cell cancers (RCC) specifically. Except for overall survival (OS), their definitions are not standardized and can be composed of different event types. Thus, end points such as relapse-free survival (RFS) or disease-free survival (DFS) can be considered composite end points as several different event types are included in their definition.

Even though these types of end points are being widely used, they are usually poorly defined and are commonly specific to each particular trial being analyzed as underlined by Mathoulin et al. [1] and by the Food and Drug Administration [2]. For example, several adjuvant trials have used different events for DFS [3]. In the S-TRAC clinical trial, comparing sunitinib and placebo for the treatment of patients at high risk of recurrent RCC, considered the following events for DFS: recurrence, secondary malignancy or death [4]. In the ASSURE phase III randomized trial, comparing sunitinib to sorafenib to placebo in patients with kidney cancer removed by surgery, considered the following events for DFS: recurrence, second primary cancer or death from any cause [5]. In the SORCE phase III double-blind randomized trial, comparing sorafenib to placebo in patients with resected primary RCC in high or intermediate risk of relapse considered the following events for DFS: local recurrence, distant metastases or death from RCC [6]. The same variations are observed in trials conducted in metastatic patients including pivotal trials that led to the registration of investigational compounds. For instance, PFS analyzed in the sorafenib registration trial, takes into account the date of progression only [7]. On the contrary, PFS analyzed in the sunitinib registration trial was calculated with the dates of progression or death from any cause [8]. The lack of clear standardized definitions for the same named end points can limit the interpretation of results when using different event types in the definition of end points in clinical trials [2, 9].

Moreover, the primary end point directly impacts trial results by affecting estimation of treatment effects and statistical power as shown by Nout et al. for breast cancer [10]. Also, in order to allow cross-comparisons of results between trials, or just to use this information in the planning of future trails, the events as well as the censoring rules need to be clearly defined for each of the events that are combined in the composite TEEs [1].

Recent publications have attempted to address this issue by proposing end point definitions in adjuvant colorectal cancer [11], in hepatocellular cancer [12] and in breast cancer [13]. However, these studies did not use an explicit consensus method. Moreover, the experts involved were not necessarily representative of the many academic groups involved in cancer trials. Moreover, to the best of our knowledge, no definition of end points has so far been proposed in kidney cancer.

This study has two main objectives: first, to better defining end points that are frequently used in adjuvant or metastatic setting for RCC patients; second, to identify the most appropriate end points and make recommendations for use in future trials. In this idea, RAND methodology, based on a large panel of experts involved in kidney cancer clinical trials, was used to provide consensus definitions on primary and secondary end points. This project is part of the DATECAN project (Definition for the Assessment of Time-to-event Endpoints in CANcer trials) whose final aim is to obtain harmonized consensus definitions for various cancer sites [14].

methods

The project was developed by the DATECAN Study Group. The methodology was first developed and applied in three tumor types, including pancreatic cancer [15], sarcoma-gastrointestinal stromal tumor [16] and breast cancer [17]. The present methodology has already been extensively described elsewhere [14].

literature review

Based on a PubMed literature search (supplementary Data S1, available at *Annals of Oncology* online), the first step involved a search to see if guidelines had not already been developed for the definitions of TEEs in kidney randomized controlled trial. After a first selection from the abstracts of the 952 articles identified, no formal consensus on the definition of TEEs was identified. Therefore, RCC was judged to be an eligible cancer type for this project.

consensus process

Formalized consensus using modified Delphi with Rand scoring methodology was used to reach consensus [18–20]. This method involves six steps: assessment of evidence; elaboration and pretesting of the questionnaire; scoring of the questionnaires; analysis of the experts' opinions and drafting of the final report; peer-review; diffusion of the recommendations (Figure 1).

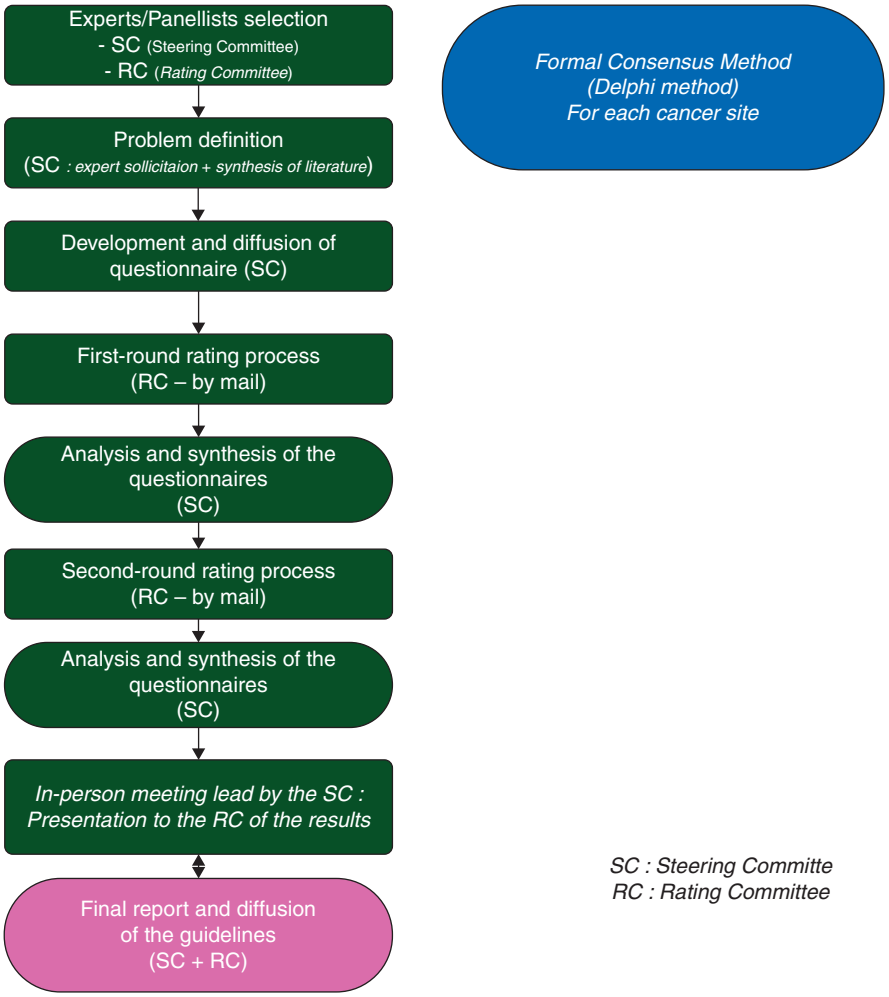

Figure 1. Modified Delphi method used to reach consensus for survival/time-to-event end points in kidney cancer trials.

questionnaires

For the first round, all Rating Committee experts (RC) received the questionnaire elaborated by the Steering Committee (SC) (supplementary Table S1, available at *Annals of Oncology* online). The RC were asked to indicate on a scale ranging from 1 (totally disagree) to 9 (totally agree) whether each event should be regarded or not as an event in the definition of each end point. At the second round, the experts scored only those items for which consensus had not been reached after the first round (supplementary Table S2, available at *Annals of Oncology* online). Based on the first round distribution of scores and their own initial score, each expert was asked to either maintain or modify their initial score. Items for which no strong consensus had been reached were discussed during an in-person meeting involving members of the SC and RC. A representative of the DATECAN Study Group led this meeting, where a preliminary draft of the recommendations was written and sent for validation to all experts.

The SC underlined the fact that defining censoring rules are statistical issues rather a clinical question. Indeed, it is common practice to classify events which are not included in the definition at the stage of the statistical analysis plan. This can lead to ignoring, censoring or treating them as competing events. As a result, censoring of other events was not discussed during the consensus process.

Following a preliminary review by the SC and RC, the first draft of the recommendations was presented to the DATECAN Study Group for approval.

results

literature search

When this project was initiated in 2010, a systematic review identified 151 publications of clinical trials in kidney cancer published between 2005 and 2009. Two disease settings were identified: metastatic/advanced (MA) and nonmetastatic (NM). Nine TEEs retained by the SC included Kidney Cancer-specific survival (KCSS), disease-free survival (DFS), relapse-free survival (RFS), metastasis-free survival (MFS), local recurrence-free survival (LRFS), local regional-free survival (LGFS), failure-free survival (FFS), progression-free survival (PFS) and time to progression (TTP).

The following events were identified: contralateral kidney cancer, appearance of metastases, local recurrence, regional recurrence, second primary invasive cancer (nonkidney), local

progression, regional progression, progression of metastases, death from kidney cancer, death related to a second cancer, death from nonkidney cancer cause, death related to protocol treatment, death from any cause and death from unknown cause. Even though not formally identified in the literature search, the SC decided to include the following events related to reasons for end of treatment: toxicity related to treatment, adverse event unrelated to treatment and patient refusal or investigator choice. Finally, loss to follow-up was also included as an event for all end points. Thus, a total of 18 distinct event types were used, not all of which were pertinent to both disease settings.

consensus rounds

Two rating rounds (first round: July 2012 to September 2012; second round October 2012 to January 2013), the in-person meeting (May 2013), and the SC meeting (March 2014) took place and led to the development of the recommendations described below.

first and second rounds

Fifty-two experts were contacted, with 36 (63.5%) and 34 (94%) participants in each round, respectively. Specialities included medical oncologists [21], radiation oncologists [2], urologists [9], hematologic oncologists [1] and biostatistician [1]. Academic groups from nine European countries were involved. Even though few biostatisticians were involved in the review process, the Pilot group was composed of three statisticians who helped in the interpretation of results. The experts were chosen for their involvement in kidney cancer trials and patient care and for their implication in interpreting results from clinical trials when choosing appropriate treatment of their patients.

Overall, experts scored 156 events pertaining to the 9 end points, 2 of which were common to both the metastatic and NM settings (KCSS and FFS). After the first round, four events relating to reasons for treatment end and loss to follow-up were no longer considered (100% consensus). Among the remaining 121 events, 31% consensus was reached, 36% (15/42) and 29% (23/79) in the metastatic and NM disease settings, respectively (Tables 1 and 2). After the second round, 43% consensus was reached, 40% (17/42) and 44% (35/79), respectively (Tables 1 and 2).

in-person meeting (Budapest, May 2013)

During the face-to-face meeting, rules for consensus allowed greater tolerance for missing or extreme scores (supplementary Table S2, available at *Annals of Oncology* online). Interesting comments raised several questions, notably the precise definition of events. Also, some end points were not considered relevant and practical in evaluating certain treatment strategies.

Other comments related to terminology such as 'survival' in those end points where this term was included, such as DFS. This may have confused some experts since events are more related to failure than survival. It also became clear that certain causes of death were difficult to classify due to ambiguity in certain items. For example, if death from any cause was excluded as an event, death related to protocol treatment and from unknown cause should also have been excluded. This ambiguity could have led to different interpretations of the events themselves by members of the RC.

Table 1. Metastatic/advanced disease setting: results of first and second rounds, face-to-face meeting

Event	End point			
	1. KCSS	7. FFS	8. PFS	9. TTP
Contralateral kidney cancer	NO	IN-2	NO	NO
Appearance of metastases	TO	IN-1	n/a	n/a
Local recurrence	TO	IN-1	n/a	n/a
Regional recurrence	TO	IN-1	n/a	n/a
Second primary invasive cancer (nonkidney)	O-1	TO	n/a	n/a
Local progression	n/a	n/a	IN-1	IN-1
Regional progression	n/a	n/a	IN-1	IN-1
Progression of metastases	n/a	n/a	IN-1	IN-1
Death from kidney cancer	IN-1	IN-1	IN-1	TI
Death related to a second cancer	O-1	NO	TO	TO
Death from nonkidney cancer cause	O-1	TO	TO	TO
Death related to protocol treatment	TI	IN-2	NO	TO
Death from any cause	TO	NO	NO	TO
Death from unknown cause	TO	TI	NO	TO

NO, no consensus; IN-1, include event first round; O-1, exclude event first round; IN-2, include event second round; O-2, exclude event second round; TI, tendency to include during face-to-face meeting; TO, tendency to exclude during face-to-face meeting; n/a, not applicable. End points: 1. KCSS, kidney cancer-specific survival; 7. FFS, failure-free survival; 8. PFS, progression-free survival; 9. TTP, time to progression.

After the face-to-face meeting, 82% consensus was reached for 103 events, 81% (34/42) and 87% (69/79), respectively (Tables 1 and 2). No consensus was reached for 18 events and concerned all end points.

Contralateral kidney cancer was the most controversial event that concerned four end points. For example, there were 13 votes to exclude and 15 votes to include this event for KCSS after the second round in both disease settings.

There were 16 votes to exclude and 13 votes to include death related to a second cancer for FFS in both settings. No consensus was reached for the following: death related to protocol treatment of PFS in the metastatic setting and RFS and LGFS in the NM setting; death from any cause for FFS and PFS in the metastatic setting and DFS, RFS and FFS in the NM setting; and death from unknown cause for PFS in the metastatic setting and MFS and LGFS in the NM setting (Tables 1 and 2).

The face-to-face meeting results were summarized by the SC in a preliminary report that was circulated for comment and approval by the RC who attended the meeting. Even after the three rounds of scoring, the consensus method revealed that intermediate TEE end points have not previously been well defined, since all of the selected end points had at least one event definition for which no consensus was obtained. The SC compiled the results in the document which was updated in October 2013 and electronically submitted to the RC who validated the final version of the recommendations. The final version was approved in March 2014 during the SC meeting.

Table 2. Nonmetastatic setting: results of first and second rounds, face-to-face meeting

Event	End point						
	1. KCSS	2. DFS	3. RFS	4. MFS	5. LRFS	6. LGFS	7. FFS
Contralateral kidney cancer	NO	IN-2	IN-2	NO	O-2	TO	IN-2
Appearance of metastases	TO	IN-1	IN-1	IN-1	O-2	O-2	n/a
Local recurrence	TO	IN-1	IN-1	TO	IN-1	IN-1	n/a
Regional recurrence	TO	IN-1	IN-1	TI	TI	IN-1	n/a
Second primary invasive cancer (nonkidney)	O-1	TO	O-1	O-1	O-1	O-1	n/a
Local progression	TO	n/a	n/a	n/a	n/a	n/a	IN-1
Regional progression	TO	n/a	n/a	n/a	n/a	n/a	IN-1
Progression of metastases	TO	n/a	n/a	n/a	n/a	n/a	IN-1
Death from kidney cancer	IN-1	IN-1	IN-2	IN-2	IN-2	IN-2	IN-1
Death related to a second cancer	O-1	TI	TO	TO	TO	TO	NO
Death from nonkidney cancer cause	O-1	TO	TO	TO	TO	TO	TO
Death related to protocol treatment	TI	IN-2	NO	TO	TO	NO	IN-2
Death from any cause	TO	NO	NO	TO	TO	TO	NO
Death from unknown cause	TO	TO	TI	NO	NO	TO	TI

NO, no consensus; IN-1, include event first round; O-1, exclude event first round; IN-2, include event second round; O-2, exclude event second round; TI, tendency to include during face-to-face meeting; TO, tendency to exclude during face-to face meeting; n/a, not applicable. End points: 1. KCSS, kidney cancer-specific survival; 2. DFS, disease-free survival; 3. RFS, relapse-free survival; 4. MFS, metastasis-free survival; 5. LRFS, local recurrence-free survival; 6. LGFS, local regional-free survival; 7. FFS, failure-free survival.

recommendations

After the face-to-face meeting, the results were compiled by the SC from the three rounds in order to come up with recommendations. The SC recommended the use of only two end points in the MA disease (Kidney KCSS, PFS) and only three end points (DFS, MFS, LGFS) in NM disease setting. The final version of the recommendations was then approved by the RC. All TEEs were defined as the time interval between the date of reference (date of inclusion, date of randomization, date of diagnosis etc.) to the end point in question. The following definitions were consensually agreed upon:

MA setting events:

- KCSS: death from kidney cancer or death from protocol treatment, whichever occurs first.
- PFS: death from kidney cancer or local, regional or metastatic progression, whichever occurs first.

NM setting events:

- DFS: death from protocol treatment or from kidney cancer or local, regional recurrence or metastases or contralateral kidney cancer, whichever occurs first.
- MFS: death from kidney cancer or appearance of metastases, whichever occurs first.
- LGFS: death from kidney cancer or local or regional recurrence, whichever occurs first.

discussion

The aim of this project was to recommend and define TEEs in kidney cancer clinical trials in both the adjuvant and metastatic disease settings using a formal consensus methodology which brought together opinions from many experts from different fields in oncology in a three-round exercise as opposed to investigator-based nonuniversal definitions for a specific treatment protocol.

A majority of trials in kidney cancer assess one or two TEEs. The most common primary end points were DFS and PFS in the adjuvant and metastatic settings, respectively. The secondary end points were generally MFS and OS in the adjuvant setting and OS or KCSS in the metastatic setting.

Until recently, precise definitions of these end points were not an issue in the adjuvant setting due to the failure of most treatments (Pal and Haas [3]). However, since results can be expected in the near future, this issue is now important. Very few face-to-face comparative trials between the seven different targeted therapies registered for metastatic renal cell carcinoma patients are available. Therefore, prescribers often balance the results of the PFS obtained with each compound throughout the different trials despite the fact that this end point does not consider the same events in every trial. One could wonder if the use of a different definition for a particular end point may affect the conclusion of these studies. It has already been shown in the context of colorectal cancer [21] and of breast cancer [10] that varying the definitions for a particular TEEs can strongly impact the estimation of time-to-event rates as well as the trial's conclusions by affecting both statistical power and estimation.

This situation reinforces the need for clear end points because intertrial comparisons or cross-trial evaluations will be done and meta-analysis could be undertaken at some point. Therefore, the adjuvant setting represents a big challenge in a highly competitive context. We thus propose to take into account our recommendations for the future analysis of these trials.

In the metastatic setting, the majority of randomized studies did not show an OS advantage, mainly due to the use of active treatments after failure of the initial therapy. It is thus important to use exact definitions for end points which will be measuring

the range of benefit that can be expected both in future trials and routine practice.

The lack of consensus regarding the definition of TEEs other than OS was confirmed by the first round results with only 31% consensus, thus underlining the variability in the end point definitions among experts involved in kidney cancer trials. For the end point 'KCSS', consensus regarding whether to include death related to protocol treatment in the end point was not reached even after the second round. This may be due to a lack of clarity in the interpretation of the event 'death due to protocol treatment'. The definition may reflect different opinions amongst experts regarding the likely impact of a treatment. The choice of a particular end point was not addressed in this paper since some end points occur earlier than others and some may be more appropriate to certain situations. For instance, it may be more appropriate to consider cancer-specific end points in elderly patients due to co-morbidities and the increased risk of death due to other causes in this population. This opinion may relate to the specialty of the expert: urologic surgeon, medical oncologist or radiotherapist, since each specialist may have a different view on the outcome of patients and consider some events irrelevant. The TEEs were selected after a literature review of published clinical trials. Although all of the 9 end points that were finally kept and better defined are frequently used, they can be relevant in specific trials dependent on the treatments under investigation. As a result, the SC identified the use of two most appropriate end points in the metastatic disease setting (KCSS, PFS) and three end points in the NM setting (DFS, MFS, LRFS).

International recommendations obtained through a formal and validated consensus process, as well as the active participation of experts from various institutions and specialties in this project, should increase the acceptability of the resulting recommendations and contribute to their wide-scale implementation in future research.

Using clearly defined and easy to use 'conservative' definitions will enable an easier endorsement and general use in the evaluation of treatment strategies and should thus contribute to avoiding misinterpretations of results, which apply to both primary and secondary end points. We suggest that the definitions of the end points, as chosen by the expert panel, should be adopted for use in future RCC clinical trials. This will ensure the interpretation of the results and facilitate the informal intertrial comparisons. Future perspectives include evaluations of the impact of the use of these definitions on results from existing or future trials in kidney cancer.

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disclosure

The authors have declared no conflicts of interest.

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appendix

DATECAN

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Breastfeeding and breast cancer risk by receptor status—a systematic review and meta-analysis

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Background: Breastfeeding is inversely associated with overall risk of breast cancer. This association may differ in breast cancer subtypes defined by receptor status, as they may reflect different mechanisms of carcinogenesis. We conducted a systematic review and meta-analysis of case–control and prospective cohort studies to investigate the association between breastfeeding and breast cancer by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status.

Design: We searched the PubMed and Scopus databases and bibliographies of pertinent articles to identify relevant articles and used random-effects models to calculate summary odds ratios (ORs) and 95% confidence intervals (CIs).

Results: This meta-analysis represents 27 distinct studies (8 cohort and 19 case–control), with a total of 36 881 breast cancer cases. Among parous women, the risk estimates for the association between ever (versus never) breastfeeding and the breast cancers negative for both ER and PR were similar in three cohort and three case–control studies when results were adjusted for several factors, including the number of full-term pregnancies (combined OR 0.90; 95% CI 0.82–0.99), with little heterogeneity and no indication of publication bias. In a subset of three adjusted studies that included ER, PR, and HER2 status, ever breastfeeding showed a stronger inverse association with triple-negative breast cancer (OR 0.78; 95% CI 0.66–0.91) among parous women. Overall, cohort studies showed no significant association between breastfeeding and ER+/PR+ or ER+ and/or PR+ breast cancers, although one and two studies (out of four and seven studies, respectively) showed an inverse association.

Conclusions: This meta-analysis showed a protective effect of ever breastfeeding against hormone receptor-negative breast cancers, which are more common in younger women and generally have a poorer prognosis than other

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