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Review

Guidelines for time-to-event end-point definitions in trials for pancreatic cancer. Results of the DATECAN initiative (Definition for the Assessment of Time-to-event End-points in CANcer trials) ☆

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Abstract **Background:** Using potential surrogate end-points for overall survival (OS) such as Disease-Free- (DFS) or Progression-Free Survival (PFS) is increasingly common in randomised controlled trials (RCTs). However, end-points are too often imprecisely defined which largely contributes to a lack of homogeneity across trials, hampering comparison between them. The aim of the DATECAN (Definition for the Assessment of Time-to-event End-points in CANcer trials)-Pancreas project is to provide guidelines for standardised definition of time-to-event end-points in RCTs for pancreatic cancer.

Methods: Time-to-event end-points currently used were identified from a literature review of pancreatic RCT trials (2006–2009). Academic research groups were contacted for participation in order to select clinicians and methodologists to participate in the pilot and scoring groups (>30 experts). A consensus was built after 2 rounds of the modified Delphi formal consensus approach with the Rand scoring methodology (range: 1–9).

Results: For pancreatic cancer, 14 time to event end-points and 25 distinct event types applied to two settings (detectable disease and/or no detectable disease) were considered relevant and included in the questionnaire sent to 52 selected experts. Thirty experts answered both scoring rounds. A total of 204 events distributed over the 14 end-points were scored. After the first round, consensus was reached for 25 items; after the second consensus was reached for 156 items; and after the face-to-face meeting for 203 items.

Conclusion: The formal consensus approach reached the elaboration of guidelines for standardised definitions of time-to-event end-points allowing cross-comparison of RCTs in pancreatic cancer.

1. Introduction

With the appearance of new types of treatments and the multiplication of lines of treatment, potential surrogate end-points for overall survival (OS) and/or intermediate end-points are being increasingly used in cancer randomised controlled trials (RCTs). These end-points are generally composite end-points such as Progression-Free Survival (PFS) or Disease-Free Survival (DFS). However, while they are being widely used, these end-points are still poorly defined and most times their definition is specific to each particular trial [1] as under-
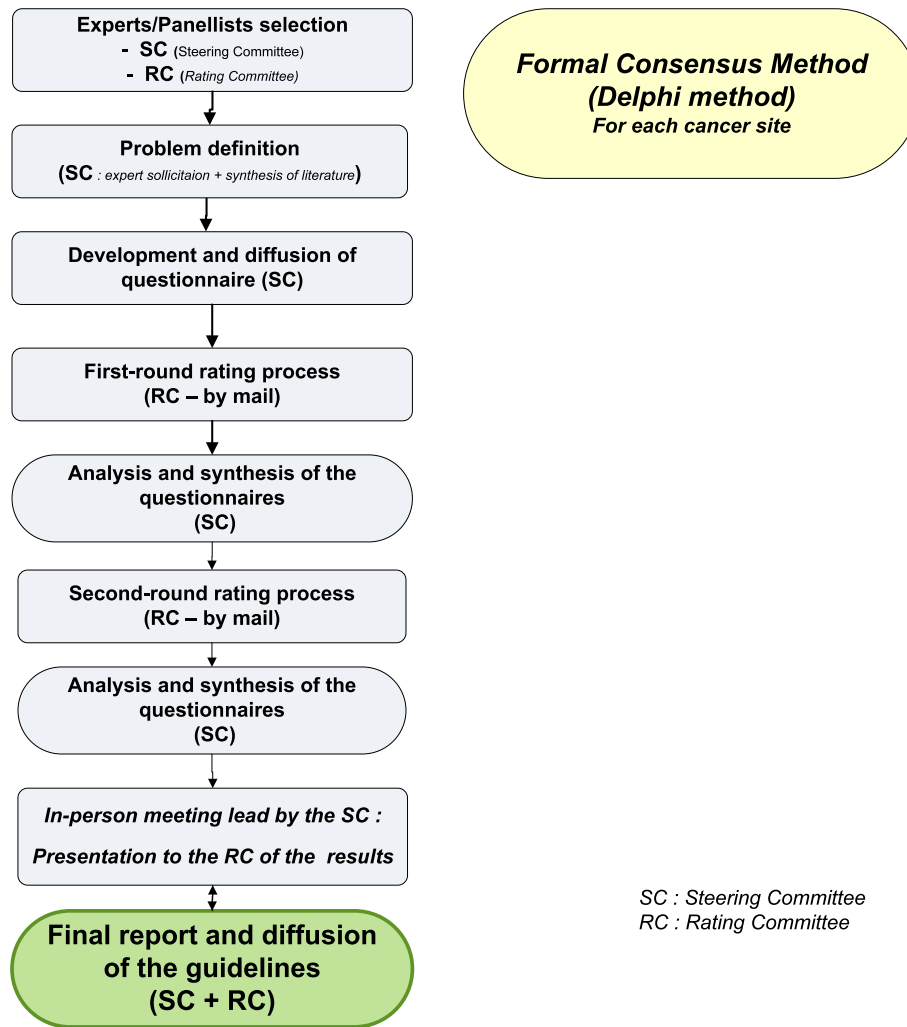
Fig. 1. Modified Delphi method used to reach consensus for survival/time-to-event end-points in pancreatic cancer randomised controlled trials.

lined by Mathoulin et al. [1] and by the Food and Drug Administration (FDA) [2]. The lack of standardised definitions clearly limits the use of these end-points as primary evaluation criteria in RCTs [2,3].

Moreover, end-point definition can directly impact trial results by affecting the estimate of treatments' effects and trials' statistical power [4].

To allow cross-comparisons of results between trials, the events and censoring rules of the composite time-to-event end-points need to be clearly defined [1].

Recent publications have already attempted to address the issue by proposing end-point definitions in adjuvant colorectal cancer [5], in head and neck cancer [6] and in breast cancer [7]. However, none of these studies has explicitly reported the use of a formal consensus building method, and involved academic groups were poorly represented in the selected panels of experts. These drawbacks may explain why the proposed definitions have been of limited use. As for pancreatic cancer, to our knowledge, no definition of end-points has so far been proposed.

We report here the first consensus built for pancreatic cancer RCTs. This report is part of the DATECAN project (Definition for the Assessment of Time-to-event End-points in CANcer trials) the final aim of which is to build harmonised consensus definitions for following cancer sites: Pancreas; Breast; Sarcoma/GIST; Stomach/oesophagus; Head and Neck; Colon/rectum; Kidney/bladder and Lung [8].

2. Methods

2.1. Protocol for consensus building

The project was developed by the DATECAN Coordinating Committee (CC). The methodology has already been extensively described by Bellera et al. [8]. We provide here a brief summary of the retained formal consensus methodology [9,10]. Major steps are summarised in Fig. 1.

Such methodology, requires the setup of three groups of medical experts: (1) a steering committee (SC) for the

Table 1
Definition of consensus for including a given event in the definition of a specific time-to-event outcome based on the distributions of the scores provided by the experts of the scoring committee at the second scoring round of the Definition for the Assessment of Time-to-event End-points in CANcer trials (DATECAN) initiative for trials on Pancreatic cancer.

Opinion on the event		Median score	Distribution of scores at the 1st round	Distribution of scores at the 2nd round
Appropriate to include the event	Strong consensus	$\geqslant 7$	All scores between 7 and 9, apart from up to 1 missing score	All scores between 7 and 9, apart from up to 3 missing scores and/or outliers <7
	Relative consensus	$\geqslant 7$	Need a second round at least one score <7	All scores between 5 and 9, apart from up to 3 missing scores and/or outliers <5
Inappropriate to include the event	Strong consensus	$\leqslant 3$	All scores between 1 and 3, apart from up to 1 missing score	All scores between 1 and 3, apart from up to 3 missing scores and/or outliers >3
	Relative consensus	$\leqslant 3$	Need a second round, at least on score >3	All scores between 1 and 3, apart from up to 3 missing scores and/or outliers >5
Uncertain	Indecision	3.5–6.5	Need a second round	Irrespective of scores
	No consensus	$\geqslant 7$	Not applicable	At least 4 scores <5 and/or missing
		$\leqslant 3$	Not applicable	At least 4 scores >5 and/or missing

literature review and selection of end-points and events and to elaborate the questionnaires; (2) a rating committee (RC), comprising at least 20 experts, in charge with scoring and analysing the questionnaires and elaborating the preliminary report and (3) a peer review committee (PRC) in charge with providing a formal and advisory opinion on the content and form of the initial version of the guideline [8]. The procedure for selecting experts (Online Table 1) has been described elsewhere [8].

3. Search strategy and selection criteria

Based on a Pubmed research, the CC first checked whether guidelines were existing for the definitions of time-to-event end-points in pancreatic cancer RCTs. Following the rules predefined by NLM (PubMed) algorithms [11], the final combinations of keywords used when the project started in 2009, was: *Consensus OR recommendation OR guidelines OR standard OR recommendations) AND (End-point or evaluation criteria OR outcome OR response criteria OR end-points OR outcomes) AND 'pancreatic' [MESH].*

In parallel, a systematic literature review was performed by the SC to retrieve all RCTs on pancreas cancer published between 2005 and 2009 and collect all reported end-points as well as the types of events considered, when available. We relied on the following algorithm [11]: *'Randomised Controlled Trial '[Publication Type] OR 'Randomised Controlled Trials as Topic' [Mesh]) AND 'pancreatic'[Mesh] AND ('2005/01/01' [PDAT]: '2009/01/01'[PDAT]) 'Meta-Analysis '[Publication Type] OR 'Meta-Analysis as Topic'[Mesh]) AND 'pancreatic'[Mesh] AND ('2005/01/01'[PDAT]: '2009/01/01'[PDAT]).*

4. Modified Delphi consensus

A modified Delphi method [12,13] was relied on to limit the consensus development process to two rounds

of questionnaires with a final in-person meeting to discuss conflicting items [14].

As for the 1st round, the questionnaire was sent electronically (electronic case report files was also proposed) to the RC members. Experts were recalled to complete the questionnaires every 3 weeks.

Based on the RAND/UCLA scoring methodology [9] for each time-to-event end-point, the RC experts were asked to indicate on a scale of integers ranging from 1 (totally disagree) to 9 (totally agree) whether the clinical events observed should be regarded as events according to the definitions of the time-to-event end-points. Scoring rules for consensus [9,10] at the 1st and 2nd round were defined in Table 1.

A descriptive statistical report was produced after the 1st round providing a list of events for which consensus has been reached (consensus to include or exclude). The SC drafted a second questionnaire including list of events for which a 2nd round was required to reach consensus. Information about the distributions of scores obtained in the 1st round (the minimum, maximum, and median scores were presented) as well their own initial score was provided.

During the 2nd round, the results of the 1st round were communicated to the RC members who were asked to score only the items for which consensus was not reached, based on the scores provided by the other experts' scoring as well as their own initial score. Each expert could thus choose to either maintain his/her initial score or to modify it.

After the 2nd round if it is concluded that no consensus has been reached regarding the inclusion/exclusion of the event further action and/or final decision concerning these items were discussed during the in-person meeting.

4.1. In-person meeting and production of guidelines

The in-person meeting involved all experts to discuss and resolve issues related to the overall coherence of the end-point definitions. If the consensus results in ascribing the same definition to be applied to two (or more)

Table 2
Time-to-event end-points considered for the elaboration of definitions and clinical events that could possibly be included in their definitions.

Time-to-event end-points
- Cancer-specific survival (no detectable disease and local detectable disease),
- Disease-free survival (no detectable disease only),
- Relapse-free survival (no detectable disease only),
- Loco-regional relapse-free survival (no detectable disease only),
- Time to local recurrence (no detectable disease only),
- Distant metastases-free survival (no detectable disease only),
- Time-to-treatment failure (all settings),
- Failure-free survival (all settings),
- Progression-free survival (detectable disease only),
- Time to progression (detectable disease only),
- Time to local progression (detectable disease only, Metastatic progression-free survival (detectable disease only),
- Time to Performance Status deterioration (all settings),
- Time to quality of life (QoL) deterioration (all settings)

Clinical events
- Local relapse/recurrence
- Local progression
- Regional relapse/recurrence
- Regional progression
- Progression of metastases/distant progression
- Appearance/occurrence of distant metastases
- Appearance/occurrence of liver metastases
- Appearance/occurrence of non-liver metastases
- Second pancreatic cancer
- Second non-pancreatic cancer
- Death related to primary cancer
- Death related to a second cancer
- Death related to protocol treatment
- Other cause of death
- Unknown cause of death
- End of treatment due to...
- Occurrence of WHO PS Grade 3-4-5
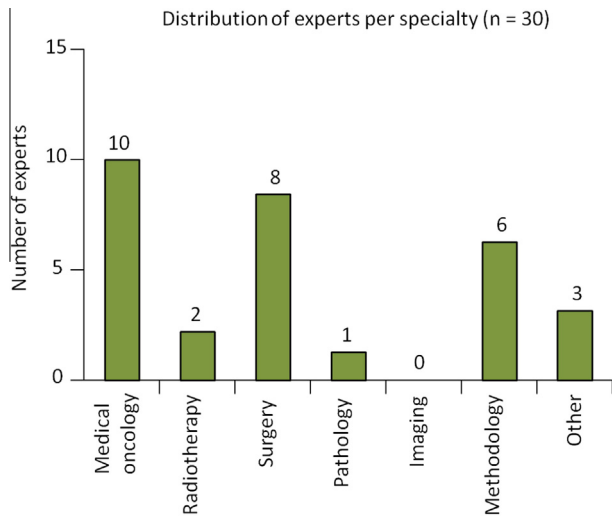- QoL score deterioration

Fig. 2.

end-points, then the end-points' terminology should be simplified and their number reduced accordingly.

Based on the meeting minutes, a preliminary draft of the recommendations was issued by the writing committee and sent for validation to the overall DATECAN panel.

Following this preliminary review, the first draft of the manuscript of guideline recommendations was sent to the PRC committee whose members provided a formal and advisory opinion on the content and form, in particular their applicability, acceptability and readability.

4.2. Academic endorsement

Finally this document was submitted for endorsement to every academic group involved in the project.

4.3. Committees' membership and information

The names of all members of the CC, SC RC and RPC involved in the pancreatic consensus, and their affiliation are reported in Online Table 1.

Academic groups from Austria, Belgium, France, Germany, Greece, Italy, Netherlands, Spain, United Kingdom and Sweden involved were:

Association des Gastro-Enterologue Oncologue (AGEO) – Arbeitsgemeinschaft Internische Onkologie (AIO) – Belgian Group of Digestive Oncology (BGDO) – Dutch Pancreatic Biliary Cancer Group – EORTC

Gastro Intestinal & Radiotherapy Groups – UNICAN-CER Gastro Intestinal group – National Cancer Research Institute (NCRI) – European Study for Pancreatic Cancer (ESPAC) – European Society for Radiotherapy and oncology (ESTRO) – Fédération francophone de Cancérologie Digestive (FFCD) – Fédération de recherché en Chirurgie (FRENCH) – Groupe coopérateur multidsicplinaire en oncologie (GERCOR) – Interdisciplinary Group for Cancer Care Evaluation (GIVIO) – Italian Group for the Study of Digestive Tract Cancer (GISARD) – Nordic Gastro Intestinal group – Sociétié Française de Radiothérapie et d'Oncologie-Swedish pancreatic – Spanish Group for studying the treatment of digestive tumors (TDD).

5. Consensus participation and consensus rates

Following the literature search for guidelines for end-point definitions, no article was retrieved and pancreas was deemed an eligible cancer site to need development of recommendations.

Two settings (no detectable disease versus detectable disease) were identified and the following 14 time-to-event end-points and 204 event types (Table 2) were retained by the SC committee and included in the questionnaire sent to the RC members.

RC experts returned the 1st and 2nd round questionnaires to the steering committee after a three-month interval on average.

After two rounds of rating (1st round: January 2011 to March 2011; 2nd round July 2011 to September 2011) and the in-person meeting (September, 23th, 2011) the recommendations were elaborated.

6. Results of the 1st and the 2nd round of scoring

Among the 52 experts contacted, 33 answered the first round (63.5%), and among them 30 also answered the 2nd round (91%).

Speciality distribution for the 30 experts involved (Fig. 2) in the two rounds was 10 medical oncologists or gastro-oncologists, two radiation oncologists, one pathologist, six methodologists or biostatisticians or epidemiologist and three other specialities (like clinical coordinators).

Overall, a total of 204 event items related to the 14 end-points were scored. After the 1st round, consensus regarding the inclusion/exclusion of an event was reached for 25 events (12%) only. After the 2nd round, consensus was reached for 156 events (76%).

7. Results of the in-person meeting (Esmo 2011, Stockholm, Sweden)

After the two rounds, no consensus was reached for 48 events distributed scattered over the 14 end-points. They were evaluated during the face-to-face (in-person) meeting. A standardised consensual definition for 13 of the 14 end-points and two possible definitions for the Time to Quality of Life Deterioration (see below) were suggested.

A consensus was obtained on the need to ensure logic and harmonisation across end-points:

(a) all deaths, irrespective of the cause, should be considered as events for the so-called 'survival end-points', except for cancer-specific survival (CSS) for which the definition is different (see above);
(b) all deaths, irrespective of the cause, should not be considered as events for so-called 'time to event end-points'.

8. Standardised definitions of time-to-event end-points

The minutes of the face-to-face meeting and decisions were summarised in a preliminary report that was circulated for comment and approval from all experts of the CC and SC committees, and from the RC experts who attended the face-to-face meeting. The document was updated in May 2012 and was submitted to the PRC who validated the final version of the recommendations. The final version was approved in November 2012. Retained definitions were summarised in the Table 3.

8.1. Cancer-specific survival (CSS) (no detectable disease and local detectable disease)

CSS is defined as the time interval between the day of reference used in the study (date of randomisation, date of diagnosis, etc) and the day of death related to primary cancer, progression, second cancer, protocol treatment or of unknown cause (Online Table 2).

Suggested definition of censoring events: Patients without any of the above mentioned events will be censored at the death from other causes or last follow up[1].

8.2. Disease-Free Survival (DFS) (no detectable disease only)

DFS is defined as time interval between the day of reference in the study (date of randomisation, date of diagnosis, etc) and the date of local relapse/recurrence or regional relapse/recurrence or occurrence of distant metastases (liver or non-liver) or appearance of 2nd pancreatic cancer[2] or death (all causes), whichever occurs first (Online Table 3).

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[1] *Last Follow-up: date of end of follow-up or data cut-off, for all endpoints including death as event, or date of last follow-up for those not including death as event.*

[2] *Require histological confirmation for patients with second non-pancreatic cancer to exclude a metastasis of the pancreatic cancer; otherwise second cancer will be included as an event.*

Table 3
Summary of consensus/no consensus decisions[§] made after the 1st and 2nd rounds and the in person meeting, by event type end-point and settings.

	No detectable disease					Detectable disease				All settings				
	DFS	RFS	LRFS	TLR	DMFS	PFS	TTP	TLP	MPFS	CSS	TTF	FFS	TPSD	TQL
Local relapse/recurrence	X	X	X	X	E						X	X	E	E
Local progression						X	X	X	E		X	X	E	E
Regional relapse/recurrence	X	X	X	X	E						X	X	E	E
Regional progression						X	X	X	E		X	X	E	E
Progression of metastases/distant progression						X	X	E	X		X	X	E	E
Appearance/occurrence of distant metastases	X	X	E	E	X						X	X	E	E
Appearance/occurrence of liver metastases	X	X	E	E	X	X	X	E	X		X	X	E	E
Appearance/occurrence of non-liver metastases	X	X	E	E	X	X	X	E	X		X	X	E	E
Second pancreatic cancer	X	E	E	E	E	X	E	E	E		X	X	E	E
Second non-pancreatic cancer	E	E	E	E	E	E	E	E	E		E	E	E	E
Death related to primary cancer	X	X	X	E	X	X	X	X	X	X	X	X	X	X
Death related to a second cancer	X	X	X	E	X	X	E	E	X	X	E	X	X	X
Death related to protocol treatment	X	X	X	E	X	X	E	E	X	X	E	X	X	X
Other cause of death	X	X	X	E	X	X	E	E	X	E	E	X	X	X
Unknown cause of death	X	X	X	E	X	X	E	E	X	X	E	X	X	X
End of treatment due to…	E	E	E	E	E	E	E	E	E		X	NC	E	E
Occurrence of WHO PS Grade 3-4-5	E	E	E	E	E	E	E	E	E		E	E	X	X
QoL score deterioration[*]													E	X
Lost to follow-up	E	E	E	E	E	E	E	E	E	E	E	E	E	E

Abbreviations: CSS, cancer-specific survival (no detectable disease and local detectable disease); DFS, disease-free survival (no detectable disease only); RFS, relapse-free survival (no detectable disease only); LRFS, loco-regional relapse-free survival (no detectable disease only); TLR, time to local recurrence (no detectable disease only); DMFS, distant metastases-free survival (no detectable disease only); TTF, time-to-treatment failure (all settings); FFS, failure-free survival (all settings); PFS, progression-free survival (detectable disease only); TTP, time to progression (detectable disease only); TLP, time to local progression (detectable disease only); MPFS, metastatic progression-free survival (detectable disease only); TPSD, time to performance status deterioration (all settings) renamed Survival with a good PS; TQL, time to quality of life (QoL) deterioration (all settings) renamed Quality of Life deterioration free survival.

[§] *Letter and colour code:* X, inclusion of the event in the end-point definition; E, no inclusion of the event in the end-point definition; NC, no consensus reached after the face-to-face meeting; empty box, event not considered for that particular end-point definition.

[*] Quality of Life (QoL) score deterioration of the targeted dimension(s) ⩾ minimal clinically important difference (MCID) as defined by the protocol according to baseline.

Suggested definition of censoring events: Patients alive and free of any of these events will be censored at the last follow-up. Other events will be ignored.

8.3. Relapse-Free Survival (RFS) (no detectable disease only)

RFS is defined as the time interval between the day of reference in the study (date of randomisation, date of diagnosis, etc) and the date of local relapse/recurrence or regional relapse/recurrence or distant metastases (liver or non-liver) or death (all causes), whichever occurs first (Online Table 4).

Suggested definition of censoring events: Patients alive and free of any of these events will be censored at the last follow-up. Other events will be ignored.

8.4. Loco-regional Relapse-Free Survival (LRFS) (no detectable disease only)

LRFS is defined as the time interval between the day of reference in the study (date of randomisation, date of diagnosis, etc) and the date of local relapse/recurrence or regional relapse/recurrence or death (all causes) whichever occurs first (Online Table 5).

Suggested definition of censoring events: Patients alive and free of all these events will be censored at the last follow-up or at the occurrence of the distant metastases (all sites) or second cancer (pancreatic or non-pancreatic). Other events will be ignored. After these events patients are no longer at risk for local or regional recurrence.

8.5. Time to local recurrence (TLR) (no detectable disease only)

TLR is defined as the time interval between the day of reference in the study (date of randomisation, date of diagnosis, etc) and the date of local relapse/recurrence or regional relapse/recurrence whichever occurs first (Online Table 6).

Suggested definition of censoring events: Patients alive and free of all these events will be censored at the last follow-up or at the occurrence of the distant metastases (all sites) or second cancer (pancreatic or non-pancreatic) or death (all causes) whichever occurs first. After these events patients are no longer at risk for local or regional recurrence.

8.6. Distant Metastasis Free Survival (DMFS) (no detectable disease only)

DMFS is defined as the time interval between the day of reference in the study (depends on the study: date of randomisation, date of diagnosis, etc) and the date of the occurrence of distant metastases (including liver and non-liver metastases) or death (all causes), whichever occurs first (Online Table 7).

Suggested definition of censoring events: Patients alive and free of all these events will be censored at the last follow-up. Other events will be ignored.

8.7. Time to treatment failure (TTF) (all settings)

TTF is defined as the time interval between the day of reference in the study (date of randomisation, date of diagnosis, etc) and the day of local or regional progression/relapse, or occurrence/progression of distant metastases (including liver and non-liver metastases) or 2nd pancreatic cancer or end of treatment (whatever causes excepted plan treatment stopping), whichever occurs first (Online Table 8).

Suggested definition of censoring events: Patients alive and free of all these events will be censored at the last follow-up or death (all causes). Other events will be ignored.

The experts underlined that theoretically this end-point could be considered more relevant for the 'detectable disease' setting since in the 'no detectable disease' and in locally advanced settings adjuvant treatment is always limited in duration.

8.8. Failure Free Survival (FFS) (all settings)

FFS is defined as the time interval between the day of reference in the study (date of randomisation, date of diagnosis, etc) and the date of local or regional progression/relapse, or occurrence/progression of distant metastases (including liver and non-liver metastases) or 2nd pancreatic cancer or end of treatment (whatever causes excepted plan treatment stopping)or death (all causes), whichever occurs first (Online Table 9).

Suggested definition of censoring events: Patients alive and free of all these events will be censored at the date of last follow-up. Other events will be ignored.

The experts underlined that theoretically this end-point could be more relevant for the 'detectable disease' setting since in the 'no detectable disease' setting adjuvant treatment is always limited in duration.

8.9. Progression Free Survival (PFS) (detectable disease only)

PFS is defined as the time interval between the day of reference in the study (date of randomisation, date of diagnosis, etc) and the date of local or regional progression or metastases progression or occurrence of distant metastases (including liver or non-liver metastases) or occurrence of 2nd pancreatic cancer or death (all causes), whichever occurs first (Online Table 10).

Suggested definition of censoring events: Patients alive and free of all these events will be censored at the last follow-up. Other events will be ignored.

8.10. Time to progression (TTP) (detectable disease only)

TTP is defined as the time interval between the day of reference in the study (date of randomisation, date of diagnosis, etc) and the date of local or regional progression or metastases progression or occurrence of distant metastases (including liver or non-liver metastases), whichever occurs first (Online Table 11).

Suggested definition of censoring events: Patients alive and free of all these events will be censored at the last follow-up or at the occurrence of second cancer or second pancreatic cancer or death (all causes) whichever occurs first. Other events will be ignored.

8.11. Time to Local progression (TLP) (detectable disease only)

TLP is defined as the time interval between the day of reference in the study (date of randomisation, date of diagnosis, etc) and the date of local or regional progression, whichever occurs first (Online Table 12).

Suggested definition of censoring events: Patients alive and free of all these events will be censored at the last follow-up or the occurrence of metastases progression or at the occurrence of distant metastases or at the occurrence of second cancer or second pancreatic cancer or death (all causes), whichever occurs first. Other events will be ignored.

8.12. Metastatic Progression Free Survival (mPFS) (detectable disease only)

mPFS is defined as the time interval between the day of reference in the study (depends on the study: date of randomisation, date of diagnosis, etc) and the date of metastases progression or occurrence of distant metastases (including liver or non-liver metastases) or death (all causes), whichever occurs first (Online Table 13).

Suggested definition of censoring events: Patients alive and free of all these events will be censored at the last follow-up. Other events will be ignored.

8.13. Time to performance status deterioration (all settings)

Survival with good Performance status (WHO PS 0 or 1 or 2) is defined as the time interval between the

day of reference in the study (date of randomisation, date of diagnosis, etc) and the day of occurrence of Grade 3-4-5 WHO PS or death (all causes) whichever occurs first (Online Table 14).

Note: Grade 5 WHO PS is death but we kept death also in the definition to achieve a clear definition.

Suggested definition of censoring events: Patients alive and free of all these events will be censored at the last follow-up. Other events will be ignored.

An additional consensus was done for the time-to-performance status deterioration which was renamed as 'Survival with a good PS (0-1-2)' to be in agreement with the general rule for end-points named 'survival' including all causes of death.

8.14. Time to Quality of Life deterioration (all settings)

1st Proposal for a final definition:

Quality of Life deterioration-free Survival is defined as the time interval between the day of reference in the study (date of randomisation, date of diagnosis, etc) and the date of occurrence of QoL score deterioration or occurrence of WHO PS Grade 3-4-5 or death (any cause), whichever occurs (Online Table 15).

Note: Grade 5 WHO PS is death but we kept death also in the definition to achieve a clear definition.

Suggested definition of censoring events: Patients alive and free of all these events will be censored at the last follow-up. Other events will be ignored.

An additional consensus was done for Time to Qualify of life deterioration which was renamed as 'Quality of Life deterioration free survival' to be in agreement with the general rule for end-points named 'survival' including all causes of death.

The experts recommend a sensitivity analysis not considering WHO PS Grade 3-4 as event since it is not a Patient Reported Outcome (PRO).

2nd Proposal for a final definition:

Quality of Life deterioration free Survival is defined as time interval between the day of reference in the study (depends on the study: date of randomisation, date of diagnosis, etc) and the day of occurrence of QoL score deterioration or death (any cause), whichever occurs first.

Suggested definition of censoring events: Patients alive and free of all these events will be censored at the last follow-up. Other events will be ignored.

9. Discussion

Using a formal consensus methodology this study resulted in the elaboration of standardised definitions and recommendations for use regarding 14 time-to-event end-points specifically designed for pancreatic cancer clinical trials. Such guidelines were inexistent before.

A majority of trials in pancreatic cancer assess one or two time-to-event end-points. The primary end-point has most often been OS, which is obviously defined as *the time interval between the day of reference in the study (date of randomisation, date of diagnosis, etc) and the date of death (all causes)*. Then most common secondary end-points or primary are DFS or PFS which definition however varied across studies. Neoptolemos et al. [14] defined, PFS (secondary end-point) as the time between randomisation and the date of local or metastatic recurrence or death (from any cause) whereas Loehrer et al. [15] defined it as the time between randomisation and the date of local or metastatic recurrence, censoring death when it was the first event. Likewise, Oettle et al. [16] defined DFS differently from Hattangadi et al. [17]. In the first case, death was considered an event while it was not in the second. Neither study considered that a second pancreatic cancer was an event for DFS, contrary to what is suggested in our consensus recommendations. One could wonder to which extent the use of a different definition for a particular end-point may affect the conclusion of these studies. Birgisson et al. [18] and Nout et al. [4] have already shown in the context of colorectal [19] and of breast cancer, respectively, that varying the definitions for a particular time-to-event end-point could strongly impact the trial's conclusions by affecting both statistical power and survival estimates.

The lack of consensus regarding the definition of time-to-event end-points was evidenced by the results of the 1st round of rating. Consensus was reached for only 12% of the items underlining how varied the expert's view on the meaning of the end-point was. As for 'cancer-specific survival', consensus regarding whether to include death related to a second cancer in the end-point definition was not reached, even after the 2nd round. This may be ascribed to a lack of clarity in attribution of death to being from second versus primary cancer but may also reflect the varying different expert's opinions amongst experts regarding the likely impact of a the tested treatment on this event, opinion that seemed to vary according to the expert's medical specialty. Different specialists may have different views on how to appraise the long-term outcome of treatments and may thus consider that some events are irrelevant. In our case, surgeons attending the face-to-face meeting considered that the risk of developing a second cancer was low in patients undergoing surgery. Globally they also considered that TTF and FFS were not adequate end-points for patients with localised disease and should only be considered in studies conducted in patients with detectable disease at the time of trial entry. All experts agreed that it was not relevant to achieve a consensus for censoring rules. Then we did not include recommendations about the censoring process. When a clinical event is not included in a definition, it can be censored,

ignored, or accounted for (using competing-risk analysis) in the statistical analysis and the selected method will be study-specific depending on objectives. Providing guidelines for events to be censored or ignored at the analysis stage is thus not straightforward. Therefore only suggestions were formulated.

A formal and validated consensus development process, such as the one reported here, may increase their chances of international recommendations of being widely adopted. Because most of the consensus process is performed by means of questionnaires that can easily be emailed or faxed, experts from institutions disseminated in various countries can be consulted rapidly and actively participate in the process. Finally, using questionnaires avoid the influence of opinion leaders that may bias the communication process, an issue that is commonly encountered in face-to-face consultation meetings. The involvement of several medical specialties, along with the involvement of a peer-review committee, should contribute to the general acceptance of the resulting recommendations, and their large-scale implementation in future research.

10. Conclusion

A formal consensus development process was used to elaborate standardised definitions of time-to-event endpoints for pancreatic cancer RCTs, allowing comparisons between trial results. This final document can be now disseminated for acquisition and endorsement by researchers and academic groups.

Extension of the DATECAN project is the ongoing DATECAN two project that will document the impact of these definitions on the results of published academic pancreatic cancer RCTs. The final objective of DATECAN two will be to validate the definition of composite end-points according the surrogate capabilities for OS.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2014.07.011.

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