

Consideration of competing risks in early setting in oncology and impact on the survival estimates: to explicitly model them? An example of a French real-world cohort in urothelial carcinoma

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Introduction

- In most of cancers diagnosed at an early and localized stage, tumor resection is the standard of care and can be potentially associated with neoadjuvant and/or adjuvant therapies (chemotherapy or immunotherapy). This is the case of muscle-invasive bladder cancer (MIUC) (1).
- Despite standard of care, patients with MIUC remain at risk of recurrence after resection. These recurrences can occur in the same anatomical region (local/locoregional recurrence (LR)), or spread to other localization (distant metastases (DM)).
- Occurrence of a DM or of LR can modify the subsequent risk of the other event. LR and DM are called competing events (CE) of each other (2).
- Should LR and DM be dependent CEs one needs to apply an appropriate statistical method, otherwise cumulative incidence estimates will be underestimated (2,3).
- The objective was to estimate DM-free survival according to 3 statistical methods:
 - The "Include" method, based on the Aalen Johansen (AJ)-based method which properly accounts for CE (4)
 - Two less optimal but commonly used approaches, which either ignore or censor competing events.

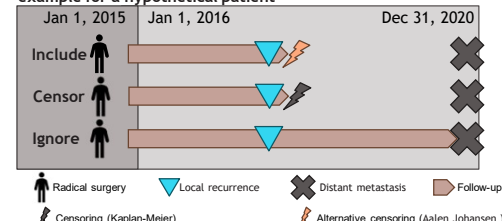
Methods

- This was a non-interventional national retrospective study using secondary data from the French National Hospitalization Database (PMSI). PMSI database exhaustively includes hospital-related claims irrespective to healthcare insurance system or hospital settings (public/private).
- The study population included all adult resectable MIUC patients who underwent a first RS (index date) in 2015. Patients were followed up from index date to December 31, 2020, or death, to assess DM-free survival (Figure 1).

- DM-free survival was defined the time from surgery to either DM or death.
- DM cumulative incidence rates (DMCIR) were reported, with 95% confidence interval (95% CI), using 3 methods (Figure 1).
- The "Include" method
 - Only data for those patients without any event are censored.
 - The cumulative incidence of each event (DM and LR) is estimated appropriately, while accounting for the presence of CE.
 - DMCIR is displayed as a CIF, based on the AJ estimator which combines a KM estimate and a risk-specific function considering the multiple events.
- The "Censor" method
 - Patients are censored at time of occurrence of CE if it occurred before the event of interest.
 - Specifically, when considering DM-free survival, if a LR is observed for a patient before the event of interest, DM-free survival will be censored at the time LR is observed.
 - By doing so, one assumes that the risk of presenting a DM for those "artificially" censored patients is similar to that of "true" censored patients (e.g., patients lost to follow-up).
 - The risk of DM is assumed not affected by the presence of an earlier LR.
 - DM-free survival is estimated using the Kaplan-Meier (KM) method.
 - DMCIR is displayed as a CIF, which is equivalent to 1-KM in the absence of CEs.
 - If the CEs are dependent, to censor at time of CE leads to informative censoring. Thus, DMCIR is overestimated.

- The "Ignore" method
 - Occurrence of CE is ignored when analyzing DM-free survival.
 - Specifically, when considering DM-free survival, if a LR is observed for a patient, this event is ignored. Only time to metastases or death (irrespective of an earlier LR) is considered.
 - By doing so, one assumes that the risk of DM is not affected by the presence of an earlier LR.
 - DM-free survival is estimated using the KM method.
 - DMCIR is displayed as a cumulative incidence function (CIF), which is equivalent to 1-KM in the absence of CEs.
 - Should the CEs be dependent, this approach leads to an overestimation of the DMCIR.

Figure 1. Study design and competing event management, example for a hypothetical patient



- The assessment of differences in DMCIR between the include method and the less optimal ones are calculated as:
 - A percentage, corresponding to the difference of DMCIR at a same time, divided by the DMCIR using the Include method.
 - The 95% CI correspond to the difference between baseline DMCIR and the lower and upper bounds of the comparator.

Results

- In 2015, 3,370 patients underwent a first radical surgery for MIUC. The mean age was 71.9 years, with 84.3% of patients being men. Full results are available elsewhere (5).
- Surgery alone was the most frequent treatment, identified among 84.9% of the patients (Table 1).

Table 1. Characteristics of the study population

Statistics		Study population (N = 3,370)
Sex ratio	Sex-ratio (% female)	5.4 (15.7)
Age at resection	Mean (SD)	71.9 (9.8)
	< 65 years (%)	22.5
	≥ 65 years (%)	77.5
Treatment	Surgery alone (%)	84.9
	Neoadjuvant therapy (%)	10.1
	Adjuvant therapy (%)	4.6
	Other (%)	0.4

- Of the 3,370 patients identified, one third (33.6%) did not present any of the event of interest (death, DM, LR) (table 2).
- Nearly half (47.8%) of the patients presented a DM at any point during their follow-up. DM was the first event identified in 37.8% of cases.
- For 377 patients (10.0%), LR was followed by DM.
- For 66 patients (2.0%), LR was followed by death (table 2).

Table 2. Distribution of the occurrence of events of interest

Statistics		Study population (N = 3,370)
No event of interest, %		33.6
Distant metastasis only, %		9.2
Local recurrence only, %		7.1
Death only, %		9.5
Local recurrence then distant metastasis (+/- death), %		10.0
Local recurrence then death (no distant metastasis), %		2.0
Distant metastasis then death (no local recurrence), %		28.6

- When comparing "Censor" method to "Include"
 - DMCIR was overestimated with the Censor method, as compared to the "Include" method
 - At 12 months, "Censor" method showed a DMCIR overestimation of 2.7 percentage points, or 9.2%.
 - At 24 months, the overestimation was 4.5 percentage points, or 11.8%, and reached 6.8 percentage points, or 14.7%, at 60 months.
- When comparing "Ignore" method to "Include"
 - DMCIR was overestimated with the Ignore method, as compared to the "Include" method.

- At 12 months, "Ignore" method showed a DMCIR overestimation of percentage 5.3 points, or 18.0%.
- At 24 months, the overestimation was percentage 8.3 points, or 21.8%, and reached percentage 11.6 points, or 25.1%, at 60 months.

Table 3. DMCIR comparison using "Include", "Censor", and "Ignore" methods (Aalen-Johansen vs 1-Kaplan-Meier)

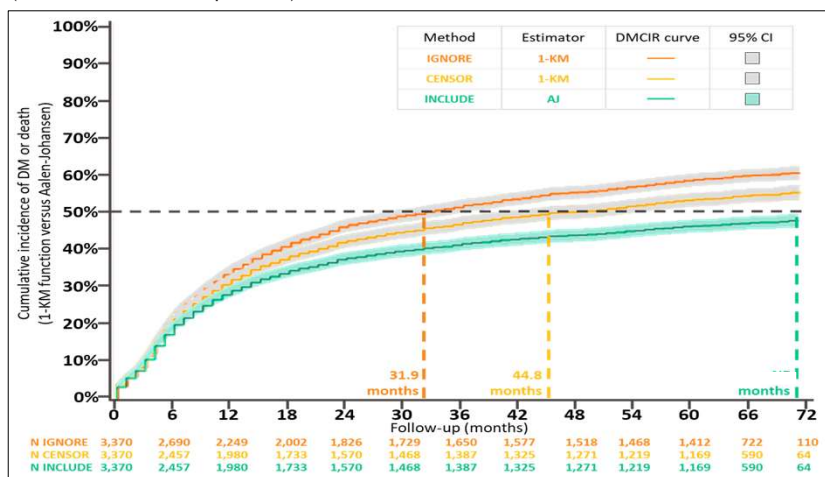
Statistics	Patients with LR (CE), n	DMCIR using INCLUDE method, % [95% CI]	DMCIR using CENSOR method, % [95% CI]	Difference vs INCLUDE, % [95% CI]	DMCIR using IGNORE method, % [95% CI]	Difference vs INCLUDE, % [95% CI]
6 months	340	20.3% [19.0 - 21.7%]	21.6% [20.2 - 23.1%]	+6.4% [-0.5 to +13.8%]	23.3% [21.9 - 24.7%]	+14.8% [+7.9 to +21.7%]
12 months	445	29.5% [28.0 - 31.0%]	32.2% [30.5 - 33.9%]	+9.2% [+3.4 to +14.9%]	34.8% [33.2 - 36.4%]	+18.0% [+12.5 to +23.4%]
18 months	501	34.7% [33.1 - 36.3%]	38.5% [36.7 - 40.2%]	+11.0% [+5.8 to +15.9%]	41.7% [40.1 - 43.4%]	+20.2% [+15.6 to +25.1%]
24 months	540	38.1% [36.5 - 39.7%]	42.6% [40.8 - 44.4%]	+11.8% [+7.1 to +16.5%]	46.4% [44.7 - 48.1%]	+21.8% [+17.3 to +26.2%]
60 months	635	46.2% [44.9 - 48.0%]	53.0% [51.4 - 55.1%]	+14.7% [+11.3 to +19.3%]	57.8% [56.4 - 59.7%]	+25.1% [+22.1 to +29.2%]
Total follow-up	643	48.0% [46.3 - 49.8%]	55.6% [53.5 - 57.5%]	+15.8% [+11.5 to +19.8%]	60.1% [58.3 - 61.8%]	+25.2% [+21.5 to +28.8%]

DMCIR: distant metastasis cumulative incidence rate, KM: Kaplan-Meier, LR: local recurrence

When comparing the median survival times with the CIF approach (Figure 2):

- Using the Ignore method, half of the patients presented with DM or death at 31.9 months.
- Using the Censor method, half of the patients presented with DM or death at 44.8 months.
- Using the Include method, less than half of the patients presented with DM or death at the end of the follow-up.

Figure 2. Distant metastasis cumulative incident rate comparison using "Include", "Ignore", and "Censor" methods (Aalen-Johansen versus 1-Kaplan-Meier)



95% CI: 95% confidence interval, DMCIR: distant metastasis cumulative incidence rate, KM: Kaplan-Meier; NE: not estimable

Conclusions

- To our knowledge, this is the first French real-world study to assess the impact of CE on an exhaustive database.
- For MIUC, occurrence of LR seems to impact the occurrence of DM: with a non-negligible proportion of patients with CE, KM-based methods overestimated CIF compared to AJ-based method. Differences increased with duration of follow-up.
- This study emphasizes the importance of using appropriate methods to account for CE when assessing survival outcomes in early-stage cancers. This trend is expected to have a growing impact with the emergence of new therapies to treat cancer at early stage.

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Acknowledgments & Disclosures

Bristol Myers Squibb (Princeton, NJ, USA) and Ono Pharmaceutical Company Ltd. (Osaka, Japan). This study was funded by Bristol Myers Squibb. All authors contributed and approved the presentation. AB, PDA, LC, FB and SBe are employees of stève consultants - a Cytel company - that has been contracted to conduct this study. CB received personal fees from Bristol Myers Squibb. FC, AFG and SBr are employees of Bristol Myers Squibb.