Modeling and comparison of non-disease-related survival using local lifetables and reported trial data: a case study from adjuvant treatment of muscle-invasive urothelial carcinoma

MSR18

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Introduction

- Estimation of non-disease-related survival (NDRS) rates in oncology are often needed for long-term survival extrapolations to avoid clinically implausible outcomes and to account for the possibility of statistical or functional cure[1,2]
- NDRS rates can also be adjusted to assist predictions of mortality rates prior to disease progression and overall survival (OS) in early treatment settings[3]
- In early treatment settings where the clinical intent is to delay the recurrence of the disease or provide a cure, flexible survival models that explicitly account for survival heterogeneity borne by long-term survivors (eg, parametric mixture models, mixture cure models) are better suited than conventional parametric models to capture the reported survival trends, but require an a priori estimation of NDRS[4,5]
- Further, reimbursement decisions for treatments in severe diseases may also depend on accurate calculations of NDRS. Recent guidance from the National Institute for Health and Care Excellence (NICE) replacing its former End of Life criteria introduced disease severity modifier for the adjustment of the effective incremental cost-effectiveness threshold in health technology assessments[6]
- The disease severity modifier is determined according to estimated quality-adjusted life-year (QALY) shortfalls for the disease population with the existing standard of care compared with the general population where the estimation of the absolute and relative QALY shortfalls may depend on the prediction of long-term NDRS rates
- Muscle-invasive bladder cancer (MIBC) is a highly aggressive cancer occurring in the muscle of the bladder wall (90%-95% cases) or in the upper excretory tract (5%-10% cases)[7-9]
- Radical cystectomy is the standard early surgical treatment modality for patients with MIBC. Despite curative potential of surgery, up to 50% of patients develop metastatic recurrence, and long-term survival rates for MIBC patients who die from non-disease-related causes are not commonly reported in the literature[10]

Objective

- To compare medium-term (10-year) and long-term (20-year) NDRS estimated from local lifetables for the patient population in the EORTC-30994 study to the reported NDRS from the trial and its extrapolations, respectively

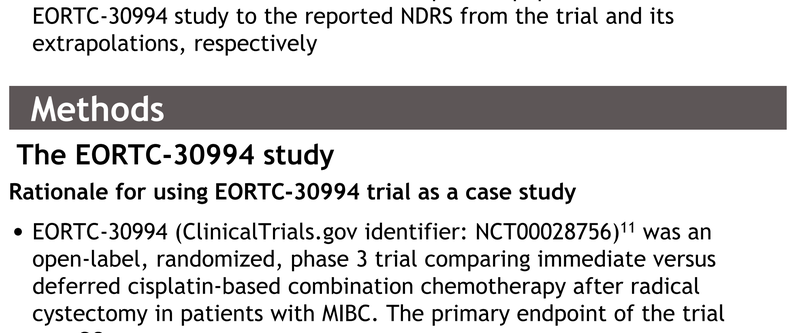
Methods

The EORTC-30994 study

Rationale for using EORTC-30994 trial as a case study

- EORTC-30994 (ClinicalTrials.gov identifier: NCT00028756)[11] was an open-label, randomized, phase 3 trial comparing immediate versus deferred cisplatin-based combination chemotherapy after radical cystectomy in patients with MIBC. The primary endpoint of the trial was OS
- Each participating clinical center in this trial across 12 European countries and Canada (**Figure 1**) prospectively chose 1 of 3 different chemotherapy regimens to be given in both arms of the study either immediately or upon relapse: methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC); high-dose MVAC, or gemcitabine plus cisplatin
- In the deferred chemotherapy arm, where median follow-up of all patients was 7.2 years, patients received no treatment until relapse. 5-year OS rate was 47.7% in the deferred treatment group, with corresponding median progression-free survival of 0.99 years and median OS of 6.74 years
- Baseline characteristics of patients in the deferred chemotherapy arm of this trial showed similarities with those of the placebo arm in the CheckMate 274 study, which showed statistically significant disease-free survival (DFS) for nivolumab over placebo in adjuvant treatment of high-risk muscle-invasive urothelial carcinoma (MIUC) patients.[12] There was a significant overlap between the observed DFS trends of the comparator arms of EORTC-30994 and CheckMate 274 trials, too

Figure 1. Distribution of enrollment across participating countries in the EORTC-30994 study



Estimation of NDRS using local lifetables

- NDRS for the EORTC-30994 trial cohort was estimated in a stepwise fashion using the country-specific lifetable data published by the World Health Organization (WHO)[13]
- Patients in the trial were enrolled between 2002-2008. Therefore, for each participating country, the mortality data available from the year of 2005 was used
- Median baseline age, and the distribution of men and women in each participating country, were assumed to be equal to the median baseline age (61 years) and the distribution of men and women (80.28% and 19.72%, respectively) reported for the overall trial population, respectively
- Conditional survival probabilities provided for the general population from the WHO website were sex-specific and provided for intervals of 5 years. For each participating country, gender-specific conditional survival probabilities were weighted with the corresponding proportions of each gender
- Sex-adjusted conditional survival probabilities in each interval were first aggregated using the enrollment shares of the participating countries in the trial and then converted to more granular weekly probabilities assuming constant hazard of death within each interval of 5 years
- Over a 20-year time horizon starting from age 61, NDRS curves were obtained by the product of age- and sex-adjusted weekly conditional survival probabilities

Estimation of NDRS using trial-reported data

- Published cumulative incidence of mortality due to all causes other than bladder cancer curves from the intervention and control arms of EORTC-30994 were digitized using WebPlotDigitizer version 4.5[14]
- Digitized data for cumulative mortality incidence were converted to survival data. After being harmonized with the reported numbers of patients at risk data, digitized non-disease-related survival data were processed by Guyot's algorithm[15] to generate corresponding pseudo-patient-level time-to-event data sets for each arm
- Following methods guidance[16,17] from NICE, standard parametric and spline-based models were independently fitted to reconstructed NDRS data to obtain long-term extrapolations. Candidate models were evaluated based on statistical goodness-of-fit criteria (Akaike information criterion [AIC] and Bayesian information criterion [BIC]) and the visual fits to the reported Kaplan-Meier curves for each endpoint
- Parametric survival functions provided better statistical fit for the data reported from the trial compared with spline-based models **(Table 1)**
- Log-normal distribution emerged as the best-fitting model for the pooled NDRS data according to AIC. When the models were ranked according to BIC, log-normal distribution provided the second-best fit
- Exponential distribution emerged as the best-fitting model for the pooled NDRS data according to BIC. When the models were ranked according to AIC, exponential distribution provided the second-best fit

Table 1. Summary of survival analysis conducted on the reported NDRS data reported from EORTC-30994 study

Model	AIC	BIC	AIC - min_{AIC}	BIC - min_{BIC}
Exponential	237.68	241.33	0.13	0.00
Weibull	238.44	245.74	0.88	4.40
Gamma	238.49	245.79	0.93	4.45
Generalized gamma	239.45	250.40	1.90	9.07
Gompertz	238.39	245.69	0.84	4.36
Log-normal	237.56	244.85	0.00	3.52
Log-logistic	238.34	245.64	0.78	4.31
Spline-1 knot hazard	239.39	250.34	1.84	9.01
Spline-2 knot hazard	239.99	254.59	2.44	13.26
Spline-1 knot normal	239.40	250.35	1.84	9.01
Spline-2 knot normal	240.55	255.15	3.00	13.82
Spline-1 knot odds	239.46	250.40	1.90	9.07
Spline-1 knot odds	240.04	254.64	2.49	13.31

min_{AIC}, minimum AIC value obtained across all candidate models; min_{BIC}, minimum BIC value obtained across all candidate models. Highlighted rows refer to the models with min_{AIC} and min_{BIC}.

Results

Figure 2. Medium-term comparison of NDRS reported from the EORTC-30994 study and estimated from local lifetables

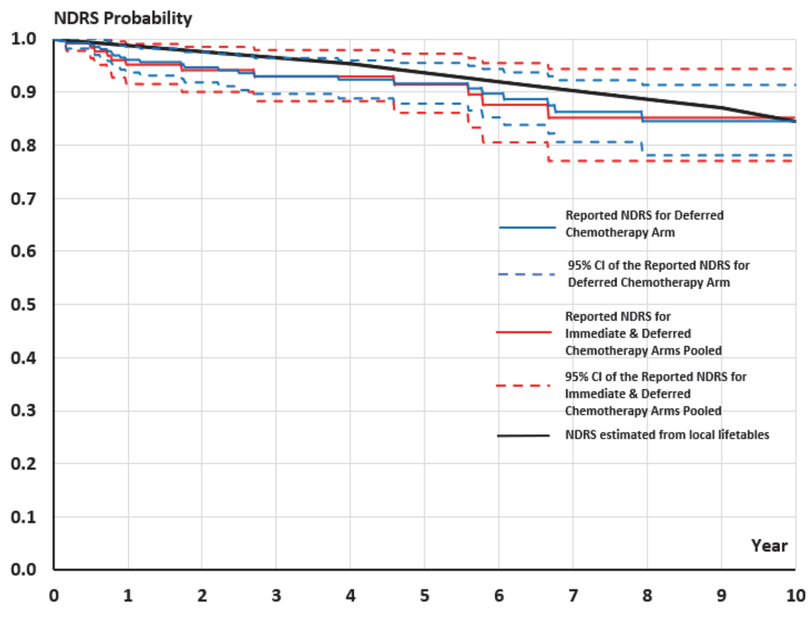
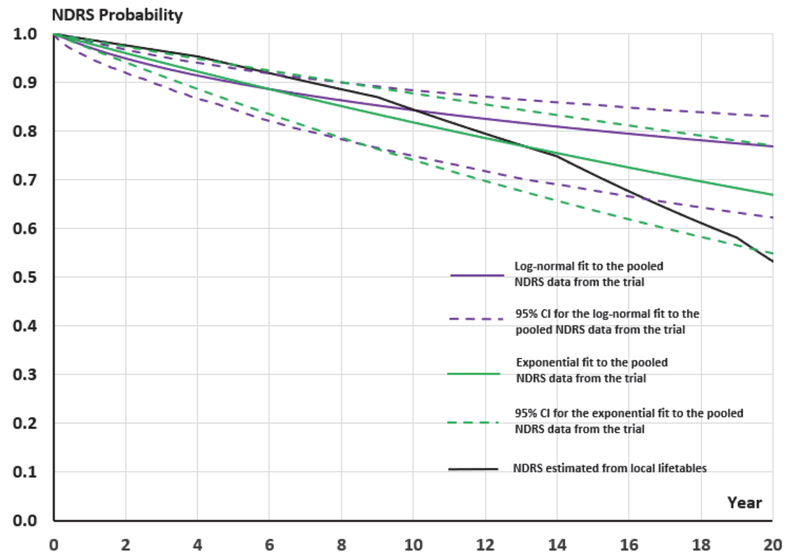


Table 2. Comparison of reported and estimated annual NDRS rates

Year	Pooled trial data across arms, %	Deferred chemotherapy arm, %	Modeled from lifetables, %
1	96.1	95.3	98.8
2	94.7	94.2	97.7
3	93.0	93.0	96.5
4	92.3	93.0	95.4
5	91.6	91.5	93.7
6	89.7	87.7	92.0
7	86.2	85.3	90.3
8	84.5	85.3	88.7
9	84.5	85.3	87.0
10	84.5	85.3	84.5

Figure 3. Long-term comparison of NDRS extrapolated from the reported data in EORTC-30994 study and estimated from local lifetables



CI, confidence interval.

Table 3. Comparison of 15- and 20-year NDRS rates estimated from extrapolations from the trial-reported data and local lifetables

	15-year NDRS rate			20-year NDRS rate		
	Point est, %	LB of 95% CI, %	UB of 95% CI, %	Point est, %	LB of 95% CI, %	UB of 95% CI, %
Log-normal[a]	80.2	67.9	85.5	76.9	62.3	83.1
Exponential[a]	74.1	63.9	82.3	67	55	77.1
Lifetables	71.3	-	-	53.4	-	-

[a]The best-fitting models to the pooled NDRS data from the trial.
Est, estimate; LB, lower boundary; UB, upper boundary.

- Over the course of the trial follow-up, there were 12 deaths in each arm due to causes that are not attributable to bladder cancer
- Estimated NDRS in the trial was negligibly different between the entire trial population and the patients in the deferred chemotherapy arm over 10 years (**Table 2, Figure 2**). The 95% confidence band for the NDRS was narrower for the entire trial population compared with the deferred chemotherapy arm
- Both exponential and log-normal distributions captured the reported trend in NDRS in the trial fairly well up to 8 years (**Figure 2**). The reported trend between years 8 and 10 was better captured by log-normal distribution; however, in the long-run beyond the follow-up, it generated more optimistic and substantially higher NDRS rates than the exponential model. For each model, point estimates for NDRS laid within the 95% confidence band of the other model over 20 years (**Figure 3**)
- NDRS rates estimated from local lifetables were higher than those reported from the trial up to 10 years, during which they laid within the 95% CI of the reported NDRS 81% of the time
- When compared with the exponential model beyond the trial follow-up (**Figure 3**), NDRS rates estimated from the local lifetables were higher up to 13.2 years. On the other hand, NDRS rates estimated from the local lifetables were higher than those estimated from log-normal model immediately after the trial follow-up
- Estimated 10-year restricted mean survival times (RMSTs) from the reported NDRS and lifetable-based NDRS were 9.09 and 9.34 years, respectively
- Estimated 20-year RMSTs from the extrapolated NDRS corresponding to exponential and log-normal models were 17.12 and 16.49 years, respectively, whereas estimated 20-year RMST from lifetable-based NDRS was 16.39 years
- Lifetable-based NDRS had an average rate gap of 0.025 versus the reported NDRS over 10 years. Compared with exponential and log-normal models over 20 years, lifetable-based NDRS had an average rate gap of 0.035 and 0.062
- Median NDRS was 20.77 years when estimated from the local lifetables. At this landmark timepoint, the median NDRS had yet to be reached in both exponential and log-normal models

Conclusions

- For MIUC patients receiving immediate or no adjuvant chemotherapy after radical cystectomy, compared with NDRS estimated from trial data, lifetable-based NDRS can be slightly optimistic in the medium term and conservative in the long term
- Estimation of NDRS from local lifetables relies on additional assumptions on the time-behavior of hazards within the 5-yearly intervals provided from the WHO and does not account for the fact that patients had a history of MIUC. Therefore, with additional data from patients undergoing radical cystectomy, precision of NDRS estimation can be improved
- Generalization of results to broader adjuvant MIUC trial settings requires further analyses with varying baseline patient characteristics

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Acknowledgments

- The study was supported by Bristol Myers Squibb
- Bristol Myers Squibb (Princeton, NJ, USA) and Ono Pharmaceutical Company Ltd. (Osaka, Japan)
- All authors contributed to and approved the presentation

Presented at ISPOR Europe 2022; November 6-9, 2022; Vienna, Austria, and virtual

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