Original Article

Comparative quality-adjusted survival analysis between radiation therapy alone and radiation with androgen deprivation therapy in patients with locally advanced prostate cancer: a secondary analysis of Radiation Therapy Oncology Group 85-31 with novel decision analysis methods

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Background: Androgen deprivation therapy in addition to radiation therapy (RT + ADT) has shown benefits in local control and progression-free survival compared with RT alone for patients with locally advanced prostate cancer in Radiation Therapy Oncology Group 85-31. However, the survival gain may be diluted with increased toxicity of ADT. The aim of the study is to compare quality-adjusted life years (QALYs) values between two groups.

Methods: We developed “quality-adjusted survival analysis using duration” (QASAD) and “quality-adjusted survival analysis using probability” (QASAP) to estimate the quality-adjusted survival time. The QASAD uses the median duration in each health state to weight the utilities, whereas the QASAP uses the proportional probability of being in each state for weighting. The survival and complication rates were reconstructed based on published Kaplan–Meier survival curves, and the utility values for states were obtained from the previous literature.

Results: QALYs values for RT + ADT were generally higher than those for RT. The QASAD resulted in a QALY value of 4.93 [95% bootstrap confidence interval (CI) = 4.12–5.71] for RT and of 5.60 (95% CI = 4.30–6.48) for RT + ADT. QASAP resulted in a QALY value of 4.85 (95% CI = 4.16–5.39) for RT and 5.39 (95% CI = 4.73–6.07) for RT + ADT.

Conclusions: We showed that RT + ADT provided slightly better quality-adjusted survival outcome than RT alone. The QASAD and QASAP methods may help the decision of optimal treatment balancing between survival gain and unfavorable quality of life.

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1. Introduction

Radiation Therapy Oncology Group (RTOG) trial 85-31 showed that long-term androgen deprivation therapy (ADT) along with standard radiation therapy (RT) improved local control and progression-free survival among patients with locally advanced prostate cancer (clinical stage T3 or N1) compared with RT alone. In an adjuvant ADT group, goserelin started during the last week of RT and continued indefinitely or until signs of progression.1 Similar clinical trials which differed only in hormonal manipulation (RTOG 86-10 and 92-02) also showed clinical benefit of additional ADT.2,3 RTOG 86-10 compared short-term ADT (2 months before and
The following assumptions were made: four health states, i.e., remission, biochemical recurrence (BCR), recurrence (radiological progression, local recurrence, or metastasis), and death, were considered. Remission included both during tumor response and no evidence of disease. In the RT group, ADT was applied only from occurrence of BCR to recurrence. In the RT + ADT group, ADT was applied from the start of treatment until recurrence. The upper time limit was 9 years as this was the follow-up time for which published data were available. The types of toxicity were RT itself and grade-2 or higher gastrointestinal or genitourinary morbidity, where the time frame of RT was retained within 2.4 months in both groups. The BCR-free, recurrence-free, and overall survival rates for both groups were available from the study by Lawton et al.\textsuperscript{1} The complication rates used in this study were taken from the pooled data of similar trials (RTOG 85-31, 86-10, and 92-02) reported in the study by Lawton et al.\textsuperscript{1} Survival and toxicity rates were indirectly extracted from reported survival curves using the Digitizelt software (version 2.0.5, Braunschweig, Germany).\textsuperscript{13} X (year) and Y (survival proportion) coordinates were digitally converted from Kaplan–Meier figure curves of RTOG 85-31 report. We used this estimated data set for analysis. Utility values were obtained from the Cost-Effectiveness Analysis Registry (available at: www.ceraregistry.org) and previous publications (Table 1).\textsuperscript{4,11}

As one-way sensitivity analyses, we calculated the QALY values for a range of plausible utility values (Table 2). Probabilistic sensitivity analysis was carried out using Monte Carlo simulation with 1,000 simulated samples. The beta distribution for utilities and the mean and standard deviation of each parameter are shown in S1 Table.\textsuperscript{16} The 95% confidence interval (CI) was estimated by bootstrapping.\textsuperscript{17}

The QASAD and QASAP calculations and sensitivity analyses were performed to integrate survival data extracted from RTOG 85-31 and plausible utilities using code developed in-house (available on request from the corresponding author) in the R programming language (http://www.R-project.org). For the combined health states and complications, the common utility estimates were obtained using the multiplicative or minimum methods.\textsuperscript{18}

3. Results

The overall QALY values obtained using multiplicative QASAD were 0.81 × 0.92 × 0.2 [under RT] + 0.92 × 1.59 [remission] + 0.79 × 2.25 [BCR] + 0.42 × 3.59 [recurrence] = 0.15 [under RT] + 1.46 [remission] + 1.78 [BCR] + 1.51 [recurrence] = 4.90 for the RT group and 0.81 × 0.793 × 0.2 [under RT] + 0.79 × 5.15 [remission] + 0.79 × 0.75 [BCR] + 0.42 × 1.82 [recurrence] = 0.13 [under RT] + 4.08 [remission] + 0.59 [BCR] + 0.76 [recurrence] = 5.57 for the RT + ADT group. Similarly, the QALY values obtained by using minimum QASAD were 4.92 for the RT group and 5.6 for the RT + ADT group. The overall QALY values obtained using multiplicative QASAP were 2.73 [remission] + 1.30 [BCR] + 0.80 [recurrence] = 4.83 and 4.16 [remission] + 0.34 [BCR] + 0.43 [recurrence] = 4.93 for the RT group and the RT + ADT group, respectively, and the QALY values obtained by using minimum QASAP were 2.75 [remission] + 1.32 [BCR] + 0.82 [recurrence] = 4.89 and 4.24 [remission] + 0.34 [BCR] + 0.44 [recurrence] = 5.02 (Table 2). In the RT + ADT group, the QALY value for the remission state was noticeably higher than that in the RT group because patients stay much longer in this state than those in the RT group.

Sensitivity analyses showed that the overall QALY values in the RT + ADT group were generally higher than those in the RT group in both the QASAD and QASAP analyses. However, the overall differences were subtle, and the differences across various health states were diverse (Table 2). The highest values across all states for the
one-way sensitivity analysis of the QASAD were noted for the RT + ADT group, indicating the superiority of this treatment. In the QASAP, RT was found to be the favorable treatment when the utility value of remission approached perfect health. The probabilistic sensitivity analysis resulted in QALY values of 4.93 (95% CI 4.90–4.96) for the RT group and 5.62 (95% CI 5.58–5.66) for the RT + ADT group when using the multiplicative QASAP method. The QALYs based on the multiplicative QASAP method were 4.85 (95% CI 4.83–4.87) for the RT group and 5.04 (95% CI 4.98–5.09) for the RT + ADT group. Fig. 1 illustrates the distributions of the QALY values obtained from the probabilistic sensitivity analyses.

4. Discussion

Most guidelines support the combination of RT with ADT based on high level evidence. Typically, ADT begins either at the beginning of RT or 2–3 months before, but the accompanying component is critical to the potency of RT. Long-term ADT, from 2 years to 3 years is recommended for locally advanced prostate cancer rather than short term (6 months). Nowadays, the role of concomitant ADT with RT is expanding as evidence is getting accumulated. Recent the Groupe d’Etude des Tumeurs Uro-Génitales (GETUG)-the Association Française d’Urologie (AFU) 16 and RTOG 9601 trials demonstrated that adding ADT during salvage RT benefits men with BCR after radical prostatectomy. However, actual combination of RT with ADT is not common in daily practice. Only 32.1% of salvage RT patients received ADT in the United States. The most likely reason is that ADT can cause many adverse effects ranging from hot flush, sexual dysfunction, diabetes, osteoporosis, and cardiovascular disease to depression and cognitive decline. Therefore, long-term use of ADT can badly affect the quality of life. Clinicians must balance the benefits and harms of ADT; therefore, we need reliable decision analysis based on quality-adjusted survival comparison.

Application of our models to RTOG trial 85–31 demonstrated that adding ADT to RT improved the quality of life. Under some extreme conditions such as assuming a perfect utility of the Remission state, adding ADT to RT does not seem to be improved the QALY values. However, the QASAD showed 3% improvements in overall QALY values and 2% improvements in QALY values obtained from the probabilistic sensitivity analyses in the RT group and 5.62 (95% CI 5.58–5.66) for the RT + ADT group. Our results were in agreement with those obtained in previous decision analyses using the Markov method, in which short-term ADT before and during RT resulted in a higher mean QALY value than RT alone (4.30 vs. 4.68) in RTOG 86–10, and 2-year additional ADT had a better mean QALY than short-term ADT + RT (4.13 vs. 3.68) in RTOG 92–02. Because the purpose of the Markov model is to incorporate all stages, the number of parameters increases with the number of stages. For this reason, a Markov model with limited number of stages is sometimes constructed. Moreover, heterogeneity and bias may be introduced when estimating parameters and performing model calibration from limited data sources. In contrast...
to the Markov method, in which many simulated estimates for transition probabilities are obtained from different data sources, our method is suitable for direct estimation of the QALY from cohort data. Another merit of our method is that it allows easy visualization of the models using decision tree diagrams. Furthermore, the QASAD and QASAP can cope with dynamic modeling components, assuming time-varying complication probabilities, and they can include discounting factors in the utilities. In our opinion, the QASAD is appropriate for diseases where the median survival time is obtainable for every state, and survival curves are characterized by an exponential shape. One such example is cancer metastasis, where the spread of cancer and corresponding stages are well defined. The QASAP is applicable to cases with long-term outcomes and possibly to more complex transitions over time-dependent complications. Because QASAP allows more flexibility in modeling perspectives than QASAD, QASAP may be more suitable for treatment comparisons in general situation. Alzheimer’s disease is such an example where patients progress through exacerbating stages of the disease and require a long-term treatment with persisting risk of complications over time. When applying Q-TWiST to RTOG 95-31 trial, there were several uncertain areas in defining states and utilities. Defining duration with toxicity (TOX) was not straightforward because adverse event could be occurred during any course of RT or ADT, and it was similar in defining TWIST because symptom- or toxicity-free period was not plausible in RT + ADT groups. Q-TWiST assumed the same utilities in BCR progression-free and recurrence-free states and could not incorporate long-term toxicity such as gastrointestinal or genitourinary.

Our new methods naturally have several limitations. First, we assumed that the states are ordered, and backward movements are not allowed in the QASAD, which is a strong assumption of the Q-TWiST method. The Q-TWiST method restricts the health states to three time frames: “time having subjective toxic side effects,” “TWIST,” and “time following systemic relapse.” In contrast, our models require no further assumptions for any health states that are naturally ordered. In the QASAP, even the constraints on irreversible states are relaxed. Furthermore, we utilized the marginal probabilities of states, whereas the Markov model intends to estimate the transition probabilities between states. As our strategy reduces the number of parameters to be estimated, the number of parameters in the QASAD and QASAP increases linearly, while the number of parameters in a first-order Markov method is quadratic in the number of states. Second, the QASAD is reliable only if the total follow-up period is long enough to estimate the median duration. If the median duration does not correctly reflect the overall survival pattern, the restricted mean duration of survival time is a possible estimate, and the QASAP is a more appropriate alternative. Third, whereas a Markov process can be defined based on an extended time horizon, our methods involve marginal movements within the states that are characterized over a fixed period for a given cohort of patients. Fourth, both the QASAD and QASAP require reliable survival statistics from cohort data. Unless high-quality survival outcome data are available, our methods are not applicable, whereas the Markov method can still be used in such a case to conduct comparisons based on conjecture or simulation. Fifth, although complication probabilities tend to be dependent, we assumed them to be independent for practical reasons as the complication probabilities for each state were not obtained for most trials.

Our method allows for elaboration. In our clinical example, as a nonparametric approach, we extracted patient data from published Kaplan–Meier survival curves. If survival is a known parametric function of time, a comparison can be made over various upper limits $T$. If certain baseline covariates are known to be associated with different prognoses, we can extend our methods using a regression model such as the proportional hazards model to account for the effect of covariates on the hazard function. To account for uncertainty of the parameter settings, it is important to address variations such as probabilistic sensitivity analyses or bootstrapped confidence intervals. When covariate information is available which provides useful information about survival patterns, one may perform subgroup analyses to explore different patterns. Finally, our method can be extended to cost analysis if utility is replaced with cost.

5. Conclusions

We developed the QASAD and QASAP as alternative quality-adjusted survival analysis methods. Our methods are readily

![Fig. 1. Probabilistic sensitivity analyses. (A) Distribution of the QALY values obtained from quality-adjusted survival analysis using duration (QASAD). (B) Distribution of the QALY values obtained from quality-adjusted survival analysis using probability (QASAP). ADT, androgen deprivation therapy; QALY, quality-adjusted life year; RT, radiation therapy.](image-url)
applicable for diseases that require survival outcome and quality-of-life assessment. Both methods represent an improvement in patient survival over various states accounting for life quality. The merit of our methods is that they incorporate time-dependent complication rates and utilities for joint health states into existing quality-adjusted survival analysis. We also demonstrated that adding long-term ADT to RT provided slightly better quality-adjusted survival outcome than RT alone using the QASAD and QASAP.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.prnil.2018.01.002.

References

1. Lawton CA, Winter K, Murray K, Machtyz M, Mesic JB, Hanks GE, et al. Updated results of the phase III Radiation Therapy Oncology Group (RTOG) trial 85–31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavorable prognosis carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2001;49:937–46.
2. Pilepich MV, Winter K, John MJ, Mesic JB, Sause W, Rubin P, et al. Phase III radiation therapy oncology group (RTOG) trial 86–10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2001;50:1243–52.
3. Lawton CAF, Lin X, Hanks GE, Lepor H, Grignon DJ, Breretton HD, et al. Duration of androgen deprivation in locally advanced prostate cancer: long-term update of NRG oncology RTOG 9202. Int J Radiat Oncol Biol Phys 2017;98:296–303.
4. Konski A, Sherman E, Krahn M, Bremmer K, Beck JR, Watkins-Bruner D, et al. Economic analysis of a phase III clinical trial evaluating the addition of total androgen suppression to radiation versus radiation alone for locally advanced prostate cancer (Radiation Therapy Oncology Group protocol 86-10). Int J Radiat Oncol Biol Phys 2005;63:788–94.
5. Konski A, Watkins-Bruner D, Breretton H, Feigenberg S, Hanks G. Long-term hormone therapy and radiation is cost-effective for patients with locally advanced prostate carcinoma. Cancer 2006;106:51–7.
6. Hsieh MH, Meng MV. Decision analysis and Markov modeling in urology. J Urol 2007;178:1867–74.
7. Kind P, Laforta JE, Matuszewski K, Raisch D. The use of QALYs in clinical and patient decision-making: issues and prospects. Value Health 2009;12(Suppl 1):327–30.
8. Neumann PJ. What next for QALYs? JAMA 2011;305:1806–7.
9. Billingham LJ, Abrams KR, Jones DR. Methods for the analysis of quality-of-life and survival data in health technology assessment. Health Technol Assess 1999;3:1–152.
10. Naimark D, Krahm MD, Naglie G, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Part 5—working with Markov processes. Med Decis Making 1997;17:152–9.
11. Cooperberg MR, Ramakrishna NR, Duff SB, Hughes KE, Sadownik S, Smith JA, et al. Primary treatments for clinically localised prostate cancer: a comprehensive lifetime cost-utility analysis. BJU Int 2013;111:437–50.
12. Elliott SP, Wilt TJ, Kuntz KM. Projecting the clinical benefits of adjuvant radiotherapy versus observation and selective salvage radiotherapy after radical prostatectomy: a decision analysis. Prostate Cancer Prostatic Dis 2011;14:270–7.
13. Gelber RD, Goldhirsh A. A new endpoint for the assessment of adjuvant therapy in postmenopausal women with operable breast cancer. J Clin Oncol 1986;4:1772–9.
14. Lawton CA, Bae K, Pilepich M, Hanks G, Shipley W. Long-term treatment sequelae after external beam irradiation with or without hormonal manipulation for adenocarcinoma of the prostate: analysis of radiation therapy oncology group studies 85–31, 86–10, and 92–02. Int J Radiat Oncol Biol Phys 2008;70:437–41.
15. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012 Feb 1;12:5. https://doi.org/10.1186/1471-2288-12-9.
16. Andrew Briggs MS, Claxton Karl. Decision modelling for health economic evaluation. Oxford University Press; 2006.
17. Elfron B, Tibshirani RJ. An introduction to the bootstrap (Chapman & Hall/CRC monographs on statistics & applied probability). Chapman and Hall/CRC; 1994.
18. Bo H, Fu AZ. Predicting utility for joint health states: a general framework and a new nonparametric estimator. Med Decis Making 2010;30:E29–39.
19. Mottet N, Bellmunt J, Bolla M, Briërs E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618–29.
20. Mohler J, Armstrong AJ, Bahnsen RR, D’Amico AV, Davis BJ, Eastham JA. Prostate cancer, version 1.2016. J Natl Compr Canc Netw 2016;14:19–30.
21. Carrie C, Hashini A, de Laroche G, Richaud P, Latorzeff I, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. Lancet Oncol 2016;17:747–56.
22. Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, et al. Radiation with or without androgen therapy in recurrent prostate cancer. N Engl J Med 2017;367:417–28.
23. Yang DD, Muralidhar V, Mahal BA, Nezolosky MD, Labe SA, Vastola ME, et al. Low rates of androgen deprivation therapy use with salvage radiation therapy in patients with prostate cancer after radical prostatectomy. Urol Oncol 2017;35:542:e25–32.
24. Rhee H, Gunter JH, Heathcote P, Ho K, Stricker P, Corcoran NM, et al. Adverse effects of androgen-deprivation therapy in prostate cancer and their management. BJU Int 2015;116(Suppl 5):3–13.
25. Sonnenberg FA, Beck JR. Markov models in medical decision making: Part 5 working with Markov processes. Med Decis Making 1993;13:322–38.
26. Welton NJ, Ades AE. Estimation of markov chain transition probabilities and rates from fully and partially observed data: uncertainty propagation, evidence synthesis, and model calibration. Med Decis Making 2005;25:633–45.
27. Cole BF, Gelber RD, Anderson KM. Parametric approaches to quality-adjusted survival analysis. International Breast Cancer Study Group. Biometrics 1994;50:621–31.
28. Cole BF, Gelber RD, Goldhirsh A. Cox regression models for quality-adjusted survival analysis. Stat Med 1993;12:975–87.