Kidney Cancer

Exploratory Subgroup Analyses of Renal Function and Overall Survival in European Organization for Research and Treatment of Cancer randomized trial of Nephron-sparing Surgery Versus Radical Nephrectomy

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Abstract

Background: In the European Organization for Research and Treatment of Cancer (EORTC) randomized trial 30904, nephron-sparing surgery (NSS) reduced the risk of renal dysfunction compared with radical nephrectomy (RN); however, overall survival was better in the RN arm.

Objective: To determine whether treatment effect on the risk of renal dysfunction and all-cause mortality differed in magnitude across levels of baseline variables.

Design, setting, and participants: This was an exploratory subgroup analysis of EORTC 30904, a phase 3 randomized trial conducted in patients with a small (≤5 cm) renal mass and normal contralateral kidney.

Intervention: Patients were randomized to RN (n = 273) or NSS (n = 268).

Outcome measurements and statistical analysis: End points included follow-up estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m², eGFR <45 ml/min/1.73 m², eGFR <30 ml/min/1.73 m², and all-cause mortality. Treatment effect was examined within baseline variables: age (<62 vs ≥62 yr), sex, chronic disease (any vs none), performance status (0 vs ≥1), and serum creatinine <1.25 vs >1.25 × upper limit of normal (ULN). Logistic and Cox regression models were used for analysis of renal dysfunction and all-cause mortality, respectively.

Results and limitations: The median follow-up periods were 6.7 yr for eGFR and 9.3 yr for survival. No variable-by-treatment interactions were significant at alpha = 0.05. For patients with baseline creatinine >1.25 × ULN (n = 36), estimated mortality hazard ratio (HR) for NSS versus RN reversed its direction (HR = 0.76, 95% confidence interval [CI]: 0.17–3.39) relative to the rest of the study cohort (HR = 1.56, 95% CI: 1.06–2.29), although this reversal was not statistically significant (interaction p = 0.25). This exploratory analysis did not reveal strong evidence of treatment effect modification in EORTC 30904, but it was limited by low power.

Patient summary: We aimed to determine whether the effect of partial versus radical nephrectomy on kidney function and overall survival depended on age, sex, and baseline health of patients enrolled in a large clinical trial. Such dependence could not be demonstrated in this analysis.

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1. Introduction

In European Organization for Research and Treatment of Cancer (EORTC) randomized controlled trial (RCT) 30904, a total of 541 patients with a small (≤5 cm) renal mass were randomized to either radical nephrectomy (RN, n = 273) or nephron-sparing surgery (NSS, n = 268), and followed for disease-specific mortality, renal function, and overall survival [1–3]. During a median follow-up of 9.3 yr, renal cancer–related mortality was uncommon in both intervention arms (RN = 1.5%, NSS = 3.0%, p = 0.23) [2]. The incidence of at least moderate renal dysfunction, as determined by an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m², was significantly reduced in the NSS arm compared with that in the RN arm [3]. With a median of 6.7 yr to last eGFR measurement, an eGFR of <60 ml/min/1.73 m² was reached by 85.7% of patients randomized to RN and 64.7% of those randomized to NSS, with a difference of 21.0% (95% confidence interval [CI]: 13.8–28.3%). Progression to severe renal dysfunction (eGFR <30 ml/min/1.73 m²) was relatively uncommon, and occurred in 10.0% of patients in the RN arm and 6.3% of patients in the NSS arm, with a difference of 3.7% (95% CI: −1.0% to 8.5%) [3].

Despite a significantly lower incidence of at least moderate renal dysfunction in the NSS arm, all-cause mortality was lower in the RN arm of this trial. With a median follow-up of 9.3 yr for overall survival, 18% of the patients in the RN arm and 25% of those in the NSS arm had died (hazard ratio 1.50, 95% CI 1.03, 2.16, p = 0.03) [2]. These findings are in disagreement with the results of most observational studies of NSS versus RN, which suggest better overall survival after NSS [4]. The findings from the EORTC RCT should not, however, be disregarded simply on the basis of disagreement with observational data because observational studies are subject to patient selection bias.

While the increased mortality in the NSS arm of this trial may realistically represent a type I error (because the p value was 0.03), the lower bound of the 95% CI for the hazard ratio, 1.03–2.16, virtually ruled out any substantial survival benefit of NSS relative to RN, at least in patients similar to those enrolled in this trial. Given that no other randomized trial of NSS versus RN is currently ongoing and EORTC trial 30904 will likely remain the only source of level 1 evidence on this subject for years to come, we have performed an exploratory subgroup analysis of available data from this study to determine whether the magnitude of the treatment effect (NSS vs RN) on the incidence of moderate and severe renal dysfunction and all-cause mortality varied as a function of baseline covariates, such as age, sex, presence of chronic disease, the World Health Organization (WHO) performance status, and baseline renal function.

2. Patients and methods

This study was a randomized trial of RN versus NSS, with all-cause mortality as the primary end point (Supplementary material). Details of the study design were reported elsewhere [1–3]. Eligibility criteria included a solitary renal mass suspicious for renal cell carcinoma ≤5 cm, a radiographically normal contralateral kidney, and a WHO performance status of 0–2. In the current exploratory post hoc analysis, four end points were examined: (1) at least one follow-up eGFR <60 ml/min/1.73 m², (2) at least one follow-up eGFR <45 ml/min/1.73 m², (3) at least one follow-up eGFR <30 ml/min/1.73 m², and (4) death from any cause (Fig. 1). The effect of randomized intervention (NSS vs RN) on these end points was examined within the strata of five baseline variables: (1) age, dichotomized at the median (<62 vs ≥62 yr), (2) sex, (3) chronic disease (any vs none), (4) WHO performance status (0 vs ≥1), and (5) baseline serum creatinine, classified as ≤1.25 × upper limit of normal (ULN) versus >1.25 × ULN. This classification of baseline renal function was necessitated by the absence of continuous subject-level creatinine or eGFR measurements at baseline, with baseline creatinine recorded only as ≤1.25 × ULN or >1.25 × ULN. No other data on baseline renal function were available in this trial. By contrast, continuous eGFR measurements were available during study follow-up for 259 of 273 participants (95%) in the RN arm and 255 of 268 (95%) in the NSS arm, with a median of nine eGFR measurements per participant in each arm, and a median of 6.7 yr to last eGFR measurement [3].

Subgroup analyses of the effect of randomized treatment on each end point were performed by fitting a regression model with treatment as the only covariate within each level of the respective baseline variable. Logistic regression models were used for analysis of the incidence of renal dysfunction, while Cox regression was used for analysis of the overall duration of survival. Tests of baseline variable-by-treatment interactions were performed by including the randomized treatment and the baseline variable of interest as covariates in the model, along with their product term. A small p value for the product term would represent evidence for a difference in the magnitude of the treatment effect across levels of the baseline variable in question. Patients with missing values for a given baseline variable were excluded from subgroup analysis involving the variable but were included in other subgroup analyses.

In addition to the subgroup analyses, multivariable analyses were performed to identify independent predictors of progression to eGFR <60 ml/min/1.73 m², eGFR <45 ml/min/1.73 m², and eGFR <30 ml/min/1.73 m², as well as independent predictors of time to death due to any cause. A separate multivariable model was fit for each of these four end points, with randomized treatment and the five baseline variables as covariates. Multivariable models were based on patients with available information on all five baseline variables. All analyses were performed in SAS version 9.3. All reported p values are two sided.

3. Results

Baseline characteristics are shown in Table 1 according to randomized treatment. The median age was 62 yr in each intervention arm, about two-thirds of all participants were

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**Fig. 1 – CONSORT diagram. eGFR = estimated glomerular filtration rate.**
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