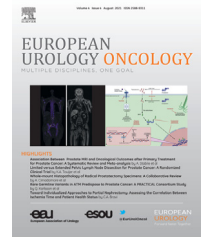


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Adjuvant Systemic Therapies for Patients with Renal Cell Carcinoma: Choosing Treatment Based on Patient-level Characteristics

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The recent results from KEYNOTE-564 [1] reinvigorated discussions on how to best interpret data from randomized clinical trials (RCTs) to determine which patients are more likely to benefit more from adjuvant therapies. KEYNOTE-564 was a phase 3 RCT that randomized patients with clear-cell renal cell carcinoma (ccRCC) to adjuvant pembrolizumab or placebo after nephrectomy. The interim analysis noted that pembrolizumab-treated patients experienced significantly better disease-free survival (DFS, the primary endpoint) over placebo-treated patients, whereas data for the key secondary endpoint of overall survival (OS) were immature [1]. This fueled debates on the utility of surrogate endpoints, such as DFS, compared with the more intuitive OS endpoint. DFS more directly captures the difference in the number of patients who may be cured by the adjuvant therapy in comparison to the control group. Furthermore, as systemic therapy options for ccRCC are rapidly increasing, death occurs progressively longer after randomization, making OS susceptible to potential confounding that may not influence DFS. Such confounding can attenuate the OS effect observed despite the presence of benefit observed for surrogate endpoints, or conversely inflate the OS benefit observed even in cases for which the new treatment is clinically inert [2,3].

Causal diagram techniques using directed acyclic graphs (DAGs) [4,5] can illustrate the above considerations (Fig. 1A, B). Consider a hypothetical RCT of adjuvant systemic therapy versus placebo in patients with ccRCC. As shown

in the DAGs, treatment choice can directly affect the probabilities of recurrence and death measured by DFS. However, the indirect effect of adjuvant treatment choice on OS is mediated by the choice of subsequent systemic therapies. The International Metastatic RCC Database Consortium score is a potential confounder for the mediating effect of subsequent systemic therapies on the original treatment choice of adjuvant therapy versus placebo. In the nonrandomized version of the trial (Fig. 1A), tumor stage is a confounder for the effect of treatment choice on recurrence. This confounding is removed by the process of randomization, as illustrated by the lack of the red arrow in the randomized version of the trial (Fig. 1B). However, confounding influences on subsequent systemic therapy choices are not removed by randomizing the original treatment choice and require statistical adjustment when estimating the effect of adjuvant treatment choice on OS. Thus, the statistical modeling used to properly estimate OS should be much more complex and rely on more assumptions than the modeling of DFS [6]. Therefore, no perfect answer can be provided in the debate regarding OS versus DFS. Both endpoints are important and should ideally point in the same direction.

In controversial scenarios such as these, our best adjudicator can be our patients and advocacy groups [7]. Survey data show that survivors with localized RCC equally value DFS and OS outcomes [8]. Although patients

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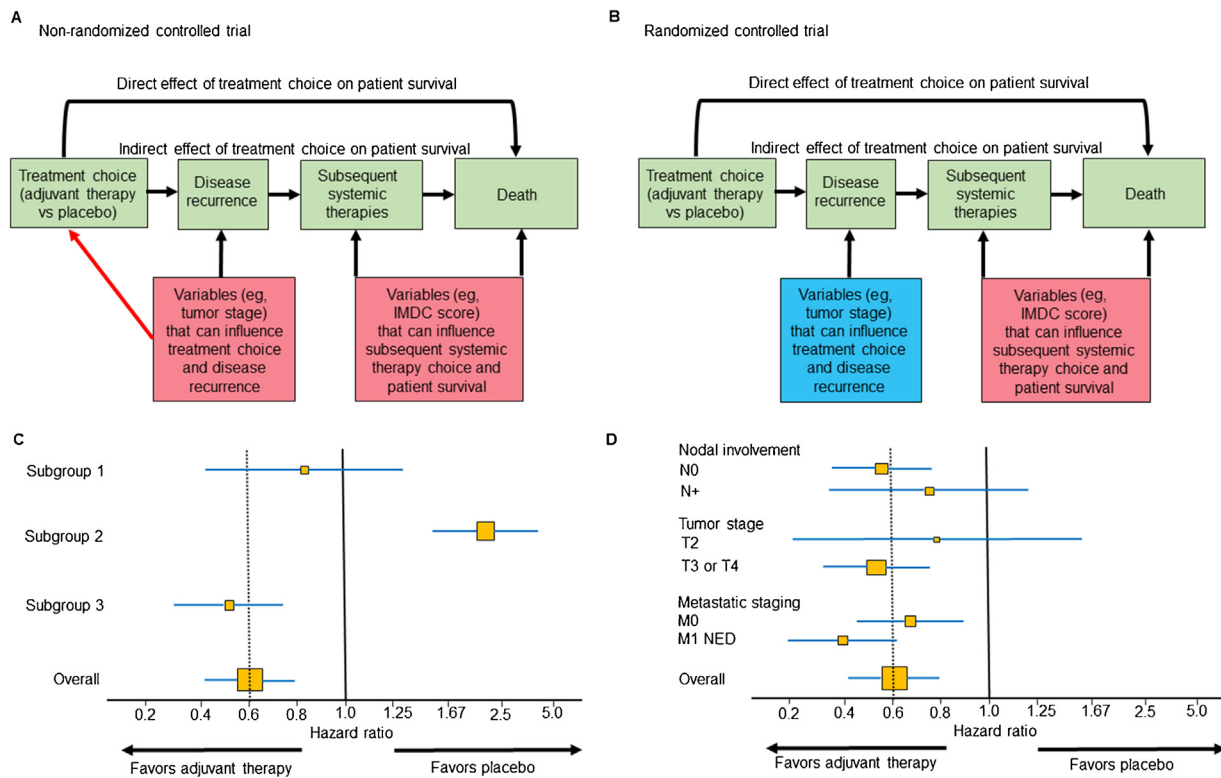


Fig. 1 – (A,B) Directed acyclic graphs for a hypothetical trial of adjuvant therapy for clear-cell renal cell carcinoma. Red boxes highlight confounders, whereas blue boxes highlight variables that can improve the power of null-hypothesis tests used to evaluate the effect of treatment choice on disease-free survival (DFS). As illustrated by the removal of the red arrow in (B), randomization renders the variable “Treatment choice” independent of any variable such as “Tumor stage”. DFS measures the direct effect of adjuvant treatment choice on the time to disease recurrence or death, and is thus unconfounded when this treatment choice is randomized. However, the overall survival (OS) endpoint accounts for both the direct and indirect effects of adjuvant treatment choice on the time to patient death. The indirect effect on the time to patient death is mediated by the choice of subsequent systemic therapies, which can still be influenced by confounding variables that need to be accounted for when estimating the effect of the randomized adjuvant treatment choice on OS. (C,D) Example forest plots looking at subgroup differences in hazard ratio estimates from a single hypothetical randomized controlled trial of adjuvant therapy versus placebo in clear-cell renal cell carcinoma. The overall treatment effect point for the trial is highlighted by the dotted vertical line. For each group of interest, the size of the yellow squares corresponds to the sample size, whereas the blue horizontal lines represent the 0.95 confidence interval. IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NED=no evidence of disease.

may choose differently depending on how each choice is framed, such biases may also affect clinicians, policymakers, and regulators themselves. During informed shared decision-making discussions for adjuvant therapies, a multidisciplinary approach between urologists and medical oncologists is warranted to properly communicate the potential risks of side effects, as well as the predicted proportions of patients who may receive such therapies even though their cancer may never recur. The advent of molecular biomarkers such as circulating tumor DNA to detect residual disease may help in selecting the patients most likely to relapse and thus benefit from adjuvant therapies [9].

Even assuming that the perfect endpoint of interest has been decided, the question becomes how to choose which patients are more likely to benefit from adjuvant therapy. The common practice of seeking that information from forest plots can be misleading [7]. From the three subgroups shown in the example forest plot in Figure 1C, only subgroup 2 is significantly different at the hazard ratio

(HR) scale from the treatment effect observed in the overall group, suggesting a multiplicative treatment-by-subgroup interaction. However, subgroup 2 scenarios may be exceedingly rare in oncology [7]. Figure 1D shows example subgroup HR estimates from our hypothetical RCT of adjuvant systemic therapy for ccRCC. The subgroups and their HR estimates intentionally resemble those seen in recent pivotal adjuvant trials in genitourinary oncology [1,10]. A common error is to conclude that because the confidence intervals for the lymph node-positive (N+) subgroup cross unity, the adjuvant treatment effect is only significant for the lymph node-negative (N0) subgroup. However, the greater statistical uncertainty due to the small number of patients in this subset yielded a wide confidence interval that crosses the dotted vertical line corresponding to the overall treatment effect. In fact, no claims of subgroup differences can be made on the HR scale for any of the subgroup HR estimates shown in Figure 1D, because they all cross the dotted vertical line and are thus statistically compatible at the 0.05 level with the overall HR estimate.

Subgroup-specific inferences can, however, still be informed by focusing instead on how each subgroup affects prognosis [7]. Patients with N+ disease are expected to have higher HRs for recurrence or death than patients with N0 disease. Thus, if the HR is stable across the subgroups, an assumption that Figure 1D does not refute, then patients with N+ disease will have a higher absolute reduction in their HR by choosing adjuvant therapy over placebo when compared to patients with N0 disease. This reasoning is compatible with the clinical intuition that adjuvant systemic therapy should be prioritized in patients with N+ over N0 disease, stage T3–4 over T2, and stage M1 with no evidence of disease over stage M0. But even these conclusions can be reversed if one chooses to focus on mean or median survival differences instead of absolute changes in the HR for DFS or OS outcomes [7]. This again makes patient input critical in deciding whether to focus on absolute differences in event rates or in mean/median survival times. Future software informed by artificial intelligence, causality theory, and rigorous statistical modeling could further assist in individualized patient risk assessment; for now clinicians and patients will together make these very complex decisions on adjuvant therapy.

Conflicts of interest: Pavlos Msaouel has received honoraria from Mirati Therapeutics, BMS, Exelixis, and Pfizer, and research funding for clinical trials from Takeda, BMS, Mirati Therapeutics, Gateway for Cancer Research, and UT MD Anderson Cancer Center, all outside of the submitted work. Petros Grivas has been a consultant for AstraZeneca, Astellas Pharma, Bayer, Bristol-Myers Squibb, Clovis Oncology, Dyana Health, Driver, EMD Serono, Exelixis, Foundation Medicine, Genentech/Roche, Genzyme, GlaxoSmithKline, Guardant Health, Heron Therapeutics, Immunomedics/Gilead, Infinity Pharmaceuticals, Janssen, Merck & Co., Mirati Therapeutics, Pfizer, Regeneron Pharmaceuticals, QED Therapeutics, Seattle Genetics, and 4D Pharma PLC; and has received institutional research funding from Bavarian Nordic, Bristol Myers Squibb, Clovis Oncology, Debiopharm, EMD Serono, GlaxoSmithKline, Immunomedics/Gilead, Kure It Cancer Research, Merck & Co., Mirati Therapeutics, Pfizer, and QED Therapeutics, all outside of the submitted work. Tian Zhang has received institutional research funding from Pfizer, Janssen, Acerta, AbbVie, Novartis, Merrimack, OmniSeq, PGDx, Merck,

Mirati, Astellas, and Regeneron; is a consultant/speaker for Genomic Health and Sanofi Aventis; has received advisory board/consulting honoraria from AstraZeneca, Bayer, Pfizer, Foundation Medicine, Janssen, Amgen, MJH Associates, Merck, BMS, Pharmacyclics, SeaGen, Calithera, Dendreon, QED Therapeutics, and Eisai; and reports stock ownership/employment (spouse) in Capio Biosciences and Archimmune Therapeutics and consulting (spouse) with Nanorobotics.

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