Disease-Free Survival as a Surrogate for Overall Survival in Upper Tract Urothelial Carcinoma

Introduction and Objective: The traditional primary endpoint in trials of perioperative systemic therapy for urothelial carcinoma is 5-year overall survival (OS). A shorter-term endpoint providing convincing evidence to allow treatment comparisons could significantly speed the translation of advances into practice. We hypothesized that disease-free survival (DFS) could be a surrogate endpoint for OS in upper tract urothelial carcinoma (UTUC) patients treated with radical nephroureterectomy (RNU).
Materials and Methods: The study included 2492 patients treated with RNU with curative intent for UTUC at 23 international institutions; 247 (10%) received adjuvant chemotherapy.
Results: Two-year/3-year DFS estimates were 78%/73% and the 5-year OS estimate was 64%. The overall agreements between 2-year and 3-year DFS with 5-year OS were 85% and 87%, respectively. Agreements were similar when analyzed in subgroups stratified by pathological stages, lymph node status, and adjuvant chemotherapy. The kappa statistic was 0.59 (95% CI 0.55-0.63) for 2-year DFS/5-year OS and 0.64 (95% CI 0.61-0.68) for 3-year DFS/5-year OS, indicating moderate reliability. The hazard ratio for DFS as a time-dependent variable for predicting OS was 11.5 (95% CI 9.1-14.4), indicating a strong relationship between DFS and OS.
Conclusions: In patients treated with RNU for UTUC, DFS and OS are highly correlated, regardless of tumor stage and adjuvant chemotherapy. While significant differences in DFS, assessed at 2 and 3 years, are highly likely to persist in OS at 5 years, marginal DFS advantages may not translate into OS benefit. External validation is necessary before accepting DFS as an appropriate surrogate endpoint for clinical trials investigating advanced UTUC patients.