Exposure group classification in an observational cohort study: Determining prostate cancer treatment for study of treatment effects on patient function

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Background and Specific Aims

Evaluating effects of therapy is often an objective in cancer outcomes research. Although a prerequisite for addressing this goal, correctly classifying patients into the appropriate group can be nontrivial in an observational, longitudinal setting with many data sources, missing or contradictory data, switching therapies, and when accounting for temporal relationships with outcome assessments.

The Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study prospectively observed over 3,000 men for over three years after being diagnosed with clinically-localized prostate cancer. A central question for the CEASAR study was how patient function changes over time after different prostate cancer treatments. Data on patient and disease characteristics and treatments received were gathered from three patient surveys given at diagnosis, 6 months, and 12 months after diagnosis, medical chart abstraction one year after diagnosis, and the SEER cancer registry. Patient-reported urinary and sexual function was measured using 0-100 domain scores from the validated 26-item Expanded Prostate Index Composite (EPIC).

For the purpose of addressing the primary research questions, treatment groups were defined as the main treatment received within the first year of therapy, irrespective of when the treatment occurred relative to the functional outcome observations at the surveys, and treatment data from the surveys and registry data were only incorporated if the patient was missing treatment information from the medical record.

The aim of the current study was to develop a new, aim-specific treatment definition and to improve capture and integration of data informing treatments received to facilitate addressing the CEASAR aims.

Approach

Three new treatment definitions were conceptualized, calculated, and compared with the former classifications: (1) the primary treatment received before the first post-treatment observation (1st PTO), (2) the primary treatment received before the second post-treatment observation (2nd PTO), and (3) the primary treatment received in the first twelve months after diagnosis.

Named-entity recognition (NER) was used to extract treatment information from free-text fields on the three patient surveys, and this information was combined with answers to the other treatment questions on the surveys.

For each of the time intervals in the new treatment definitions, we determined whether patients had each of four treatment types (radical prostatectomy, radiation, ablation, and hormones) and the associated date. The patient was classified as having had the treatment if any of the five data sources indicated he had, and the corresponding treatment date was obtained using the first nonmissing date found in a hierarchical order of the five sources: chart, six-month survey, twelve-month survey, registry, baseline survey, where the hierarchy was determined based on expected reliability by clinical experts. If there was no evidence of receipt of any active treatments in the given time interval, the patient was classified as having active surveillance (AS), in which case the date of treatment start was set to the diagnosis date.

Furthermore, temporal order of treatments found to have occured before the given survey was ascertained. Clinical experts created a mapping of different treatment sequences to five primary treatment classifications according to treatment-attribution goals of CEASAR Aim 1.

The new variables were compared with original treatment assignments, and the number and types of discrepancies were tabulated. The new treatment start dates were compared with the old via mean squared error.

Results

The new treatment assignment corresponding to the 1st PTO was different from the original treatment variable in 334 patients in the CEASAR analytic cohort. (119 of those were previously set to missing but now set to AS.) 90 patients who previously did not meet inclusion criteria for the primary analysis were included based on their new treatment classification, and 23 patients who were previously in the cohort were now excluded. Among the patients that had the same treatment assignment for both the original variable and the 1st PTO, the mean squared error of the original time since treatment start date was 1713 days, assuming the new 1st PTO and associated dates are correct. 47 of those dates were exactly one year or one month off (+/-). About 123 patients had different treatment assignments at their two survey times, 44 switching from observation to surgery, and 36 switching from observation to radiation.

Using the new treatment definitions and calculation, the estimates for the mean group differences comparing radical prostatectomy with AS in sexual function at twelve months post-treatment changed from -29.1 [95% CI: -32.8, -25.5] to -28.4 [-31.9, -25.0]. The group difference in urinary incontinence changed from -18.8 [-21.6, -16.0] to -18.3 [-21.0, -15.6].

Orig. tx	Surg only	Rad only	Abl only	Horm only	AS only
Surgery	1474	6	0	1	50
Radiation	18	930	0	9	32
Ablation	0	2	55	0	2
Hormone	3	1	0	46	2
AS	10	9	2	7	400
Missing	7	4	1	3	90

Orig tx	Abl;Rad	Horm;Surg	Horm;Rad	AS;Surg	AS;Rad	AS;Abl	AS;Horm
Surgery	0	2	0	28	0	0	0
Radiation	0	0	5	1	24	0	0
Ablation	1	0	0	0	0	1	0
Hormone	0	0	3	0	0	0	0
AS	0	0	0	8	6	0	8
Missing	0	0	0	7	6	0	1

Significance

Classifying patients into treatment groups can be complex when integrating many data sources with conflicting and missing information, and cursory assignments can lead to incorrect classifications which can alter research study results by introducing bias and spurious variance in effect estimates. Care must be taken to precisely define the exposure variable in a way appropriate for the given analysis and accounting for temporal relationships with the outcome measurement.