JOURNAL OF GERIATRIC ONCOLOGY XX (2016) XXX–XXX

Available online at www.sciencedirect.com

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Validity of Adjuvant! Online in older patients with stage III colon cancer based on 2967 patients from the ACCENT database

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ARTICLE INFO

Article history:
Received 16 March 2016
Received in revised form
13 May 2016
Accepted 7 July 2016

Keywords:
Colorectal
Older
Adjuvant
ACCENT

ABSTRACT

Background: Adjuvant! Online is a tool used for clinical decision making in patients with early stage colon cancer. As details of the tool's construction are not published, the ability of Adjuvant! Online to accurately predict outcomes for older patients (age 70+) with node positive colon cancer receiving adjuvant chemotherapy is unclear.

Methods: Individual data from older patients with stage III colon cancer who enrolled into multiple trials within the ACCENT database were entered into the Adjuvant! Online program to obtain predicted probabilities of 5-year overall survival (OS) and recurrence-free survival (RFS). Median predictions were compared with known rates. As co-morbidities were not known for ACCENT patients, but required for calculator entry, patients were assumed to have either "minor" or "average for age" co-morbidities.

Results: 2967 older patients from 10 randomized studies were included. When "minor" co-morbidities were assumed, the median predicted 5-year OS rate of 64% nearly matched the actual rate of 65%; when "average for age" co-morbidities were assumed, the median prediction dropped to 58%, outside the CI for the actual rate. On the other hand, assuming

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http://dx.doi.org/10.1016/j.jgo.2016.07.002
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Please cite this article as: Papamichael D, et al, Validity of Adjuvant! Online in older patients with stage III colon cancer based on 2967 patients from the ACCENT database, *J Geriatr Oncol* (2016), http://dx.doi.org/10.1016/j.jgo.2016.07.002

"minor" co-morbidities gave a median 5-year RFS prediction of 62%, outside the 95% CI for the actual rate of 58%, while assuming "average for age" co-morbidities yielded a better median prediction of 57%.

Conclusion: Adjuvant! Online is reasonably accurate overall for predicting outcomes in older trial patients with stage III colon cancer, though accuracy may differ between 5-year RFS and 5-year OS predictions when a fixed degree of co-morbidities is assumed.

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1. Introduction

Colorectal cancer is one of the most commonly diagnosed cancers with a worldwide incidence of >1,000,000 per year,[1] and the probability of developing the disease increasing substantially in the 7th decade of life.[2] The majority of patients with stage I or II colon cancer are cured by surgery alone, while patients with stage III disease are normally considered for adjuvant chemotherapy after surgery. At present, oxaliplatin-based combination chemotherapy is considered standard of care for such patients.[3–6] However, a recent report from the ACCENT database suggested reduced benefit from combination chemotherapy in the adjuvant setting for patients aged 70 or older compared to the use of single agent fluoropyrimidines.[7] Indeed, it may be difficult to distinguish survival gains between adjuvant treatments as patients grow older, mostly due to competing risks of death from other causes.

The Adjuvant! Online colon cancer calculator provides probabilities for recurrence-free survival, relapse, overall survival, death from cancer, and death from other causes by 5 years post-treatment, both with and without chemotherapy.[8] Input values include age (in years), sex, co-morbidities (minor, average for age, and three levels of major), tumor stage (T1, T2, T3, T4), number of positive nodes (0, 1–3, 4–10, >10), number of nodes examined (0, 1–3, 4–10, >10), histologic grade (1, 2, 3), and treatment (none vs. 5FU-based vs. oxaliplatin-based). Although reportedly based on a large sample from the population rather than data from clinical trials, this tool does not include additional demographic and disease variables such as race, BMI, performance status, and tumor location; furthermore, the methodology and internal/external validation of this calculator has not been published by its authors. In 2011, Gill et al. compared the performance of Adjuvant! Online and Numeracy[9] web calculators in predicting outcomes for patients with stage II and stage III disease using a population dataset and patient data from two clinical trials.[10] In this study, the authors concluded that the calculators showed equivalent accuracy for patients treated with surgery and 5FU, while Adjuvant! Online yielded more accurate predictions for patients treated with surgery alone. The Numeracy calculator was subsequently replaced by an ACCENT-derived prognostic calculator for stage III patients, which showed enhanced predictive ability relative to Numeracy in an external validation.[11] Despite lack of transparent model publication and other apparent limitations, the Adjuvant! Online calculator is well known and widely used. It remains unclear whether Adjuvant! Online can accurately predict outcomes for older patients with node positive colon cancer who received adjuvant single agent or combination chemotherapy.

2. Materials and Methods

2.1. ACCENT Database

The Adjuvant Colon Cancer Endpoints (ACCENT) database contains patient-level information on more than 30,000 patients enrolled to 25 adjuvant colon cancer trials since 1977.[12–15] All clinical trials included had IRB approval. Endpoints in ACCENT include overall survival (OS), defined as the time from randomization to death due to any cause, and recurrence-free survival (RFS), defined as the time from randomization to disease recurrence or death due to any cause. The present analysis focuses on the subset of patients with stage III disease who were aged 70 years or older (Table 1).

2.2. Adjuvant! Online Predictions

For each older patient in ACCENT with stage III disease, the following characteristics were entered into the Adjuvant! Online calculator: age (in years), sex (male, female), tumor stage (T1, T2, T3, T4), tumor grade (1, 2, 3), number of examined lymph nodes (1–3, 4–10, >10), number of positive lymph nodes (1–3, 4–10, >10), and chemotherapy (none, 5FU/LV, or FOLFOX). From these entries, estimated probabilities of 5-year OS and 5-year RFS were obtained and recorded. Because degree of co-morbidities (minor, average for age, or major) is a required calculator entry, but not recorded with the ACCENT database, both "*average for age*" and "*minor*" co-morbidities were considered in two separate analyses. This was felt appropriate, considering that these were patients who were entered into clinical trials, and unlikely to have major co-morbidities. No definition is provided by the Adjuvant! Online calculator for the different degrees of co-morbidity. Also, data collection procedures for the N0147[15] and C08[14] trials did not distinguish between grade 1 versus grade 2 tumors; to address this, these sub-categorizations were randomly imputed for patients with tumors described as "low" grade at rates equal to those otherwise observed in ACCENT.

2.3. Statistical Methods

Distributions of patient and disease characteristics and treatment were summarized descriptively within the analysis set of elderly ACCENT patients. Concordance between predicted and actual 5-year OS and 5-year RFS status from Adjuvant! Online and actual patient outcomes were assessed as follows. First, for each endpoint, the median 5-year predicted probability was computed across ACCENT patients and compared with the

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