EUROPEAN JOURNAL OF CANCER 47 (2011) 990–996

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Two or three year disease-free survival (DFS) as a primary end-point in stage III adjuvant colon cancer trials with fluoropyrimidines with or without oxaliplatin or irinotecan: Data from 12,676 patients from MOSAIC, X-ACT, PETACC-3, C-06, C-07 and C89803

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ARTICLE INFO

Article history:
Received 20 September 2010
Received in revised form 10 December 2010
Accepted 15 December 2010
Available online 21 January 2011

Keywords:
Colon cancer
Adjuvant therapy

ABSTRACT

Background: The ACCENT group previously established disease-free survival (DFS) with 2 or 3 years median follow-up to predict 5 year overall survival (5 year OS) in stage II and III colon cancer. ACCENT further proposed (1) a stronger association between DFS and OS in stage III than II, and (2) 6 or 7 years necessary to demonstrate DFS/OS surrogacy in recent trials. The relationship between end-points in trials with oral fluoropyrimidines, oxaliplatin and irinotecan is unknown.

Methods: Associations between the treatment effect hazard ratios (HRs) on 2 and 3 years DFS, and 5 and 6 years OS were examined in 6 phase III trials not included in prior analyses from 1997 to 2002. Individual data for 12,676 patients were analysed; two trials each tested oxaliplatin, irinotecan and oral treatment versus 5-FU/LV.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.12.015

Clinical trial end-points
Disease-free survival

Findings: Overall association between 2/3 year DFS and 5/6 year OS HRs was modest to poor (simple R^2 measures: 0.58–0.76, model-based R^2: 0.17–0.49). In stage III patients, the association increased (model-based $R^2 \geqslant 0.79$). Observed treatment effects on 2 year DFS accurately 5/6 year OS effects overall and in stage III patients.
Interpretation: In recent trials of cytotoxic chemotherapy, 2 or 3 years DFS HRs are highly predictive of 5 and 6 years OS HRs in stage III but not stage II patients. In all patients the DFS/OS association is stronger for 6 year OS, thus at least 6 year follow-up is recommended to assess OS benefit. These data support DFS as the primary end-point for stage III colon cancer trials testing cytotoxic agents.

1. Introduction

Colorectal cancer is the third most common cancer in the United States, with approximately 145,000 new cases diagnosed annually. In patients whose disease is detected at a point where surgical cure is possible but risk of recurrence remains high (stage III), randomised clinical trials have demonstrated that adjuvant chemotherapy reduces the likelihood of recurrence and leads to long-term improvements in overall survival.[1,2] Adjuvant therapy for stage II patients remains controversial but such patients have frequently been included in clinical trials with stage III patients.

Based on a pooled analysis of individual patient data from 18 randomised clinical trials testing 5-FU based treatment, the Adjuvant Colon Cancer End-points (ACCENT) Group previously established that the end-point of disease-free survival (DFS), assessed after 3 years median follow-up, is a valid surrogate end-point for 5-year overall survival (OS).[3] Subsequent work suggested that DFS with 2 years median follow-up may also be an appropriate end-point, and that the association between treatment effects on DFS and OS was stronger in patients with stage III than II disease, however both of these findings required further confirmation.[4]

In the last 10 years, multiple new agents (irinotecan, oxaliplatin, bevacizumab, cetuximab and panitumumab) have been demonstrated to extend survival in patients with colorectal cancer following disease recurrence. In the trials used in the initial ACCENT analysis, which were conducted in the pre-combination therapy era, the median time from recurrence to death was 12 months; currently, this median time is approximately 2 years,[5] which suggests that follow-up times of greater than 5 years may be required to observe OS benefits from therapy in more recent or future trials.[6] This prediction has proven accurate for the MOSAIC trial which tested the FOLFOX regimen versus 5-FU/LV, where 6 years of follow-up were required to attain statistical significance for the OS end-point.[7]

In the period since the collection of the original 20,898 patient ACCENT database, multiple additional large trials in the adjuvant setting have been completed and now have mature OS data available (Table 1). The goal of this analysis, using the individual patient data from these six trials not used in the original analysis, was to (1) confirm that DFS remained an appropriate end-point for adjuvant colon cancer trials, (2) validate DFS with 2 years median follow-up as an end-point with similar predictive properties as 3 year DFS, (3) to confirm that the association between HRs based on DFS and OS was stronger in stage III than stage II patients and (4) to assess whether longer follow-up would strengthen the surrogacy between DFS and OS in more recent trials where median survival following recurrence is extended.

2. Methods

The methods used in this study are a continuation of those previously used by the ACCENT Group.[3] For the present analysis, ACCENT identified and obtained individual patient data from 6 phase III adjuvant colon clinical trials not included in prior ACCENT analyses (Table 1). These trials accrued patients between 1997 and 2002, involved 12,676 patients, and included 12 distinct treatment arms (six 5-FU/LV control treatment arms, six experimental arms – two combining oxaliplatin with 5-FU/LV, two combining irinotecan with 5-FU/LV and two using oral fluoropyrimidine regimens). DFS was defined as the time from randomisation to the first event of either disease recurrence or death due to any cause. OS was defined as the time from randomisation to death due to any cause. Based on inconsistent long-term follow-up between trials (trial follow-up not mandated past 6 years), for all trials except the C-06 and X-ACT trials data were censored at 6 years from randomisation; sufficient follow-up was available for the C-06 trial to allow censoring at 8 years from randomisation, and for the X-ACT trial all data was used for analysis as for that trial follow-up status was uniformly established on all patients at the date of trial completion.

The primary goal of this analysis was to test the association between the treatment effects on DFS assessed after 2 or 3 years median follow-up (2 year DFS and 3 year DFS, respectively) and the treatment effects on OS assessed after 5 or 6 years median follow-up (5 year OS and 6 year OS). For all analyses, efforts were made to replicate actual clinical trial conduct, where patients enter over a period of several years, and thus at any given calendar date have differing durations of follow-up. For each analysis conducted at a specific time point (e.g. 3 years), the outcome data for each patient were censored at the point in time at which the median trial-level follow-up was 3 years. For example, if a trial accrued evenly over a period of 3 years, then the median follow-up would be 3 years after 1.5 years had elapsed from the close of randomisation. At this point, the first patient enrolled would have 4.5 years of follow-up, whereas the last patient enrolled would have 1.5 years of follow-up.

Table 1 – Trials included.

Trial	Accrual period	# Patients	Experimental treatment arm	% Stage III
MOSAIC[14]	1998–2001	2246	FOLFOX4	60
X-ACT[15]	1998–2001	1987	Capecitabine	100
NSABP C-06[16]	1997–1999	1557	Uracil/tegafur	53
NSABP C-07[17]	2000–2002	2434	FLOX	71
CALGB 89803[18]	1999–2001	1264	IFL	100
PETACC-3[19]	2000–2002	3188	FOLFIRI	71

Key: FOLFOX = oxaliplatin, bolus and infusional 5-FU, leucovorin; FLOX = oxaliplatin, bolus 5-FU, leucovorin; IFL = irinotecan, bolus 5-FU, leucovorin; FOLFIRI = irinotecan, infusional 5-FU, leucovorin.

Treatment effects were measured by the hazard ratios within each trial comparing experimental and control arms for each end-point. Based on findings in the original ACCENT analysis,[4] the current analysis was conducted overall in patients and separately by stage, using methods previously described.[3] Sub-analyses by risk group within stage, such as for 'high-risk' stage II patients, were not possible due to differences in data collection between the 6 included trials. The primary measures used to assess the association between DFS and OS were (1) the correlation of HRs from each of the six within-study comparisons between the DFS and OS end-points (assessed as the R^2 value from a weighted linear regression on within trial HRs from separate Cox proportional hazards models for the two end-points, referred to as the 'simple' association), and (2) the trial level association from a formal surrogacy model, measured by the trial-level surrogacy measure known as the copula R[28] (referred to as the model-based association). Both measures range from 0 to 1, with values close to zero indicating poor association whereas a value of 1 indicates perfect association. The formal surrogacy model uses the individual patient data to estimate the relationship between the risk of a DFS and OS event. Predicted HRs (with 95% prediction intervals) for OS were calculated based on the model previously established based on the original 18 ACCENT trials,[3] using the observed HRs for DFS within each of the current six trials.

This work was funded by a grant from the US National Cancer Institute to the Mayo Clinic to support the North Central Cancer Treatment Group. The funding source played no role beyond providing funding for this project. This project was reviewed and approved by the Mayo Clinic Institutional Review Board.

3. Results

3.1. Overall association

Of the 12,676 patients, 9395 (74%) were stage III and 3250 (26%) were stage II. The median follow-up on living patients (by reverse Kaplan–Meier) was 6 years. The pattern of recurrence in the six trials was consistent with expectations, with 83% of recurrences occurring in the first 3 years (Fig. 1). In this set of trials conduced from 1997 to 2002, the median survival following recurrence was 20 months.

Considering all trials and all patients, the association between DFS assessed at either 2 or 3 year median follow-up and OS with 5 or 6 year median follow-up was moderate

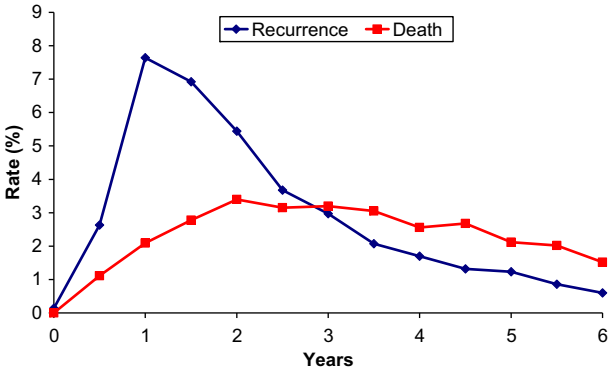

Fig. 1 – Risk of recurrence in each 6 month interval following randomisation among those remaining recurrence free at the start of each interval, by years for randomization.

(Table 2), with the simple R^2 association between hazard ratios values ranging from 0.58 to 0.76 between the DFS and OS end-points. However, the model-based R^2 values indicated poor association, ranging from 0.17 to 0.49. This association between the DFS end-points was poor for both 5 year OS and 6 year OS.

3.2. Association in stage III patients

Based on the previous work of the ACCENT group which demonstrated the association between DFS and OS end-points was stronger in stage III than stage II patients, we assessed the association between the end-points in the six new trials when limited to stage III patients. In the stage III patients, 69% (2327/3392) and 84% (2852/3392) of patient recurrences occurred in the first 2 and 3 years, respectively (compared to 57% (259/455) and 77% (351/455) in stage II patients), and median survival following recurrence in patients with stage III disease was 19 months (compared to 29 months in stage II patients).

When restricted to patients with stage III disease, the association between DFS and OS was strong for all time points considered, with the simple R^2 association ranging from 0.89 to 0.93, and the model-based R^2 association from 0.79 to 0.88 for the various end-points (Fig. 2, Table 2). Specifically, for example, the simple R^2 association between 2 year DFS and 5 year OS was 0.91, and the model-based association

Table 2 – Association between 2 and 3 year DFS with 5 and 6 year OS, for all patients and stage III patients only.

DFS years	OS years	All patients		Stage III patients	
		WLS R^2 (95% CI)[a]	Copula R^2 (95% CI)	WLS R^2 (95% CI)[a]	Copula R^2 (95% CI)
2	5	0.58 (0.02–1.00)	0.37 (0.00–0.98)	0.91 (0.54–1.00)	0.86 (0.64–1.00)
2	6	0.76 (0.37–1.00)	0.49 (0.00–1.00)	0.93 (0.60–1.00)	0.88 (0.70–1.00)
3	5	0.60 (0.04–1.00)	0.20 (0.00–0.78)	0.93 (0.78–1.00)	0.81 (0.54–1.00)
3	6	0.75 (0.33–1.00)	0.17 (0.00–0.72)	0.89 (0.74–1.00)	0.79 (0.50–1.00)

[a] The confidence intervals of WLS R^2 were calculated based on 1000 bootstrap samples.

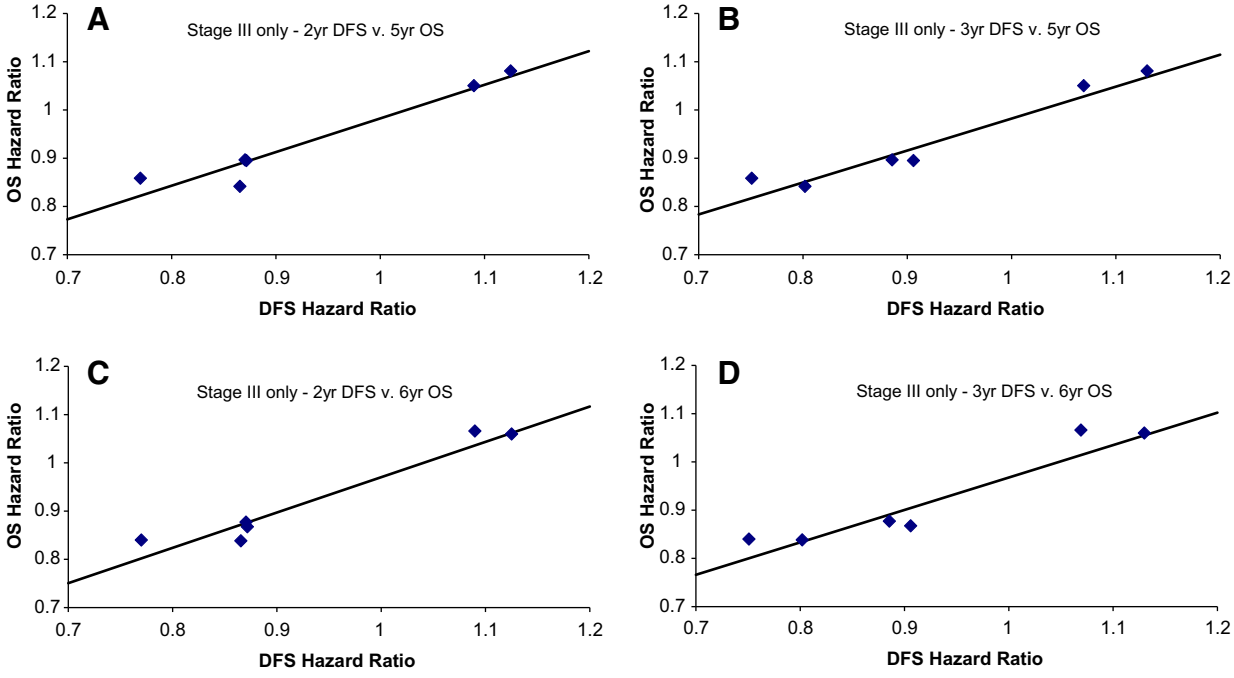

Fig. 2 – Hazard ratios for 2 and 3 year DFS versus 5 and 6 year OS, stage III patients. (A) 2 year DFS versus 5 year OS. (B) 3 year DFS versus 5 year OS. (C) 2 year DFS versus 6 year OS. (D) 3 year DFS versus 6 year OS.

was 0.86 (95% confidence intervals (CI) 0.64–1.00). There was no meaningful difference in association in the stage III patients whether DFS was assessed at 2 or 3 years median follow-up, or whether OS was assessed at 5 or 6 years median follow-up.

Four of the six trials included patients with stage II disease. When analyses were restricted to stage II patients from these four trials, the association between DFS after either 2 or 3 median years follow-up and OS with either 5 of 6 years follow-up was poor (simple R^2 association <0.50 for all associations, model-based associations could not be estimated).

3.3. *Predictive model validation*

Based on data from the 18 trials included in the original ACCENT publication, a trial-level weighted regression model for predicting the within trial OS HR based on the within trial DFS HR was proposed, both overall and for only stage III patients.[3,4] We used this model, with the observed DFS HRs after 2 years median follow-up from the new six trials to predict the OS results at the 5 and 6 year time points in stage III patients (Table 3, Fig. 3). The observed trial level hazard ratio for the OS comparison after 6 years median follow-up was within the 95% prediction limits predicted by the model using 2 year DFS for all six of the trials. Similar results were observed for the model using 2 year DFS to predict 5 year OS as well as for the model using the 3 year DFS time point to predict 5 year OS (data not shown). However the observed trial level HR for 6 year OS was within the 95% prediction limits from model based on the 3 year DFS for only three of the six new trials (data not shown). Within the combined stage II and III cohort, 5 and 6 year OS results were within the 95% prediction limit based on 2 year DFS for all six new trials. Three year DFS predicted (within 95% confidence limits) five and four of the six new trials for 5 year OS and 6 year OS, respectively.

4. Discussion

Based on individual patient pooled analyses of trials conducted from 1977 to 1999 using 5-FU based treatment, the ACCENT Group previously validated the DFS end-point, measured at a time point of 3 years median follow-up, as a valid surrogate end-point for 5 year OS. The use of the DFS end-point has allowed for the faster completion of clinical trials, which in turn

Table 3 – 95% Prediction intervals for hazard ratios for 5 and 6 years OS based on observed 2 year DFS hazard ratio, stage III patients.

Trial	Observed 2 year DFS HR	Predicted 5 year OS HR (95% CI)	Observed 5 year OS HR	Predicted 6 year OS HR (95% CI)	Observed 6 year OS HR
1	0.77	0.82 (0.73–0.92)	0.86	0.82 (0.75–0.90)	0.84
2	0.87	0.91 (0.83–0.99)	0.90	0.90 (0.84–0.96)	0.88
3	1.09	1.09 (0.96–1.22)	1.05	1.08 (0.98–1.17)	1.07
4	0.87	0.90 (0.82–0.99)	0.84	0.90 (0.83–0.96)	0.84
5	1.13	1.12 (1.01–1.23)	1.08	1.10 (1.02–1.19)	1.06
6	0.87	0.91 (0.83–0.99)	0.90	0.90 (0.84–0.96)	0.87

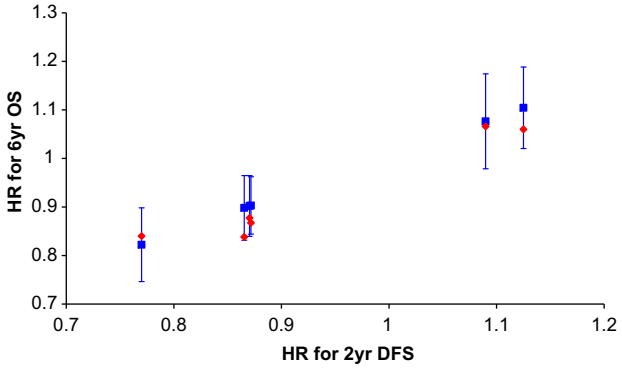

Fig. 3 – Model-based predictions and actual hazard ratios, 2 year DFS as a predictor for 6 year OS, stage III only.

has allowed more rapid regulatory approval of agents and ultimately allowed effective treatments to reach patients more quickly. In subsequent analyses using the original ACCENT dataset, 2 year DFS was observed to have similar predictive ability to 3 year DFS for long-term OS, and the association between DFS and OS was found to be stronger in patients with stage III versus stage II disease. The strong association between 2 year DFS and long-term OS can be explained by the fact that most cancer recurrences occur within the first 2 years, particularly in patients with initial stage III disease.

In the time period since the mid 1990's, multiple active agents have been introduced for the treatment of recurrent colon cancer. In large part due to the efficacy of such agents, the median survival following cancer recurrence has increased from approximately 12 to, in the studies included in this present analysis, 20 months. This increase in median survival following recurrence will likely diminish the association between DFS assessed after a median follow-up of 2 or 3 years and 5 year OS, potentially requiring longer follow-up to detect an OS benefit since patients are living longer after recurrence.[6] In addition, adjuvant therapy for stage III disease is now based on combination therapy including oxaliplatin, and includes the possibility of oral therapy with capecitabine.[9] Whether the association between DFS and OS is maintained in the presence of these newer treatment options in the advanced disease and adjuvant setting remained an open question.

Here, we have obtained and analysed data from the six major international trials conducted from 1997 to 2002, which thus have relatively mature OS follow-up, and which were not included in the initial ACCENT analysis. These analyses clearly demonstrate that for trials with exclusively stage III disease patients and cytotoxic therapy, the association between DFS assessed after 2 or 3 years median follow-up and OS remains intact. The results from these trials do not definitively dictate whether 2 year DFS or 3 year DFS should be 'preferred', based on the present data either end-point is an appropriate option. Based on the prediction models, 2 year DFS provided somewhat more accurate predictions for 5 and 6 year OS. However, as demonstrated by de Gramont et al. through simulation[6] and in the MOSAIC trial in practice,[7] 6 or 7 years median follow-up for OS may be required to detect a survival benefit, and thus to demonstrate a strong relationship with 3 year DFS.

The present analysis leaves unanswered the question of whether DFS at an early time point will accurately predict later OS results in a trial in stage II colon cancer or a trial which includes a large proportion of stage II patients. The results after 6 years of median follow-up do not support a strong association, however, in simulations, 7 years of follow-up for OS was found to improve the association between the two end-points.[6] In the current dataset, 38% (175/455) of patients with stage II disease whose disease had recurred remained alive at the censoring time point for the current analysis. Ultimately most of these patients will succumb to their recurrence, thus with extended follow-up the association between treatment effects on DFS and OS could improve. However, as when compared to stage III patients, stage II patients have both longer survival following recurrence,[10] and have a higher likelihood of death without recurrence,[4] in trials of stage II patients alone the association between DFS and OS will likely never be statistically robust. For example in the MOSAIC trial, despite a trend towards improved DFS in stage II patients after 3 years follow-up, absolutely no benefit in OS was observed at the 6 year time point.[7] Unless DFS is considered a clinically relevant end-point on its own merits, analyses based on data to date support the use of OS as the most appropriate end-point for trials in unselected stage II disease.

Clinical trials in adjuvant colon cancer now include the possibility of both chemotherapeutic and biologic agents. Such new therapies may only delay, as opposed to prevent, recurrence. This paradigm is strongly suggested by the results of the C-08 trial which tested bevacizumab in addition to FOLFOX therapy in patients with stage II and III disease. In C-08, there was strongly suggestive evidence of an early reduction in recurrence risk in the first year of therapy, while the bevacizumab was being delivered, which disappeared once treatment was stopped and thus after three years of follow-up no significant DFS benefit was observed.[11] In a trial where the agent being tested may have such a mechanism of action (delay as opposed to prevent recurrence), the use

of short-term end-points such as DFS must be carefully considered.[12] Uncertainty in the impact of a therapy argues for a longer-term DFS end-point, such as 3 year or even 4 year DFS as opposed to 2 year DFS. In addition, the end-point must allow adequate time past the completion of a therapy to assess the delay versus prevention of recurrence hypothesis. While no data is available to provide a firm recommendation, we recommended a DFS end-point that is assessed at least 2 years after the completion of protocol therapy.

An important limitation of this analysis is that it is based on only 6 trials. Analyses of surrogate end-points with a limited number of trials are known to suffer from large variability in estimation, which likely was manifest in our analysis of the pooled stage II and III patients where the model-based and simple R^2 measures differed greatly.[13] However, given the size and complexity of adjuvant colon cancer trials, these 6 trials are the entire population of large trials conducted world-wide in this time period, and as such provide the best available evidence. The ACCENT group will continue to work with individual trial lists to include data from newly maturing adjuvant trials, such as the XELOXA trial.[9]

In summary, in this analysis of six trials of 12,676 patients added to the ACCENT database, we have validated that for trials in patients with stage III disease testing cytotoxic therapies, results based on DFS assessed after 2 or 3-year median follow-up are valid and appropriate primary end-points. In trials that include a substantial proportion of stage II patients, at the present time data are inadequate to provide confidence that 2 or 3 year median follow-up results will accurately predict OS results at 5 or 6 years. As median survival following recurrence continues to improve, all adjuvant trials should follow patients for at least 8 years to allow a complete assessment of OS, which remains an end-point of clinical importance despite the fact that in the elderly population, competing causes of death take on a greater role as follow-up duration increases. The strong association observed based on previous and current studies, as well as the lengthy required follow-up and associated confounding for OS in recent trials, supports DFS as the most appropriate end-point for adjuvant clinical trials in patients with stage III colon cancer treated with both 5-FU based cytotoxic chemotherapy regimens.

Conflict of interest statement

None declared.

Acknowledgement

Funded by NCI Grant CA-25224 to the Mayo Clinic to support the North Central Cancer Treatment Group.

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