An initial watch and wait approach is a valid strategy for selected patients with newly diagnosed metastatic colorectal cancer

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Received 7 March 2012; revised 30 April 2012; accepted 7 May 2012

Background: A range of treatments are available for patients with metastatic colorectal cancer (mCRC). An initial period without active treatment, a 'watch and wait approach', is variably employed in routine practice; however, there is no data to support this approach.

Patients and methods: We prospectively collected data regarding clinician treatment recommendations for patients with newly diagnosed mCRC in addition to subsequent treatment and outcomes. Follow-up and management was according to standard protocols.

Results: Seven hundred and thirty-six patients (59.1% male, 40.9% female) with mCRC (January 2003–December 2010) were analysed; the median age was 67.9 years (range 26.2–95.5). Three hundred and seventy-seven patients (51.2%) received immediate chemotherapy. For 133 (18.1%), treatment was considered inappropriate. 34 patients (4.6%) declined therapy. For 192 (26.1%), a watch and wait policy was adopted and 168 (87.5%) of these received treatment, at a median of 3.7 months (range 2–35 months) from diagnosis. Compared with patients immediately treated, the number receiving all active chemotherapy agents (30.4 versus 39.3%) was similar and median survival (27 versus 17 months, \( P=0.0008 \)) was superior.

Conclusions: Our study demonstrates that a substantial minority of patients underwent an initial watch and wait approach. Ultimately, they received a similar treatment exposure to patients treated immediately and the survival outcomes were not compromised.

Key words: delayed treatment, metastatic colorectal cancer, watch and wait

Introduction

Colorectal cancer is one of the most common cancers diagnosed worldwide [1, 2]. About 40% of patients present with either advanced disease or develop recurrence after initial treatment of early-stage tumours [3]. A broad range of treatment options are now available, with current guidelines [4] recommending initial chemotherapy for all patients, either single agent or combination treatment, according to patient’s status.

Where treatment is not initiated when metastatic disease is diagnosed, specific concerns are that patients may miss a window of opportunity and thereby never receive treatment, or may receive treatment at a time point where, due to deteriorating Eastern Cooperative Oncology Group Performance Status (ECOG PS) or increasing disease bulk, it is less effective. Delaying treatment may also potentially compromise survival by reducing the opportunity to be exposed to treatment with all active agents [5]. However in routine practice, clinicians may consider the option of watchful waiting before initiating active therapy for selected patients, specifically those with asymptomatic, low volume and surgically incurable disease.

No previously reported series describes how frequently a watch and wait strategy is pursued in routine practice, or the outcome. Here, we present data from a multisite series where initial clinician decision-making was prospectively documented, and comprehensive clinical details, treatment received and survival outcomes were analysed.
methods
Prospective data were collected from four Melbourne hospitals (Royal Melbourne Hospital, Melbourne Private Hospital, Western Hospital and Western Private Hospital). Data analysis was supported by BioGrid Australia. Initiated in 2003, the consensus dataset for all patients included detailed data related to diagnosis and management of metastatic disease and outcomes. Patients were routinely discussed in a multidisciplinary meeting and a consensus opinion was reached after review of clinical features, pathology and imaging. However, ultimate treatment recommendations were at the treating clinicians’ discretion after consultation with the patient and consideration of patient preferences. For all patients with metastatic disease, the treating clinicians documented treatment recommendations at initial diagnosis and patient acceptance of this advice. All patients were treated either on a clinical trial, if available, or according to the standard protocols. Hospital ethics committees approved analysis of this data.

A database search identified all patients diagnosed with metastatic colorectal cancer (mCRC) between January 2003 and December 2010 at participating hospitals, including patients with metastatic disease at initial diagnosis and those with recurrence after initial presentation with early-stage disease. Individual hospital medical records were reviewed when required.

As summarised in Table 1, ‘immediate treatment’ was defined as treatment recommended and planned to commence within 1 month of the decision to pursue treatment. Patients declining a recommendation to commence treatment were encouraged to attend follow-up appointments to further discuss the possibility of treatment at a later date.

A ‘watch and wait’ plan was defined as a recommendation to not initiate immediate treatment at the time of diagnosis of metastatic disease. For all medical oncologists, this was considered an appropriate option for patients with low bulk and asymptomatic disease, where progression at known sites of disease was considered unlikely to cause rapid clinical deterioration, and for patients considered likely to reliably attend follow-up appointments (standard protocols were for clinical review at 4 weeks and repeat imaging at 8 weeks to define the extent of disease progression). In each case, the intent was to initiate treatment at a later time, either at clinicians’ discretion (due to tumour factors such as significant disease progression or the development of bulky or symptomatic disease) or at patients’ discretion (a desire to pursue active treatment).

Where a watch and wait plan was recommended, patients were also offered immediate treatment and were included in the group corresponding to their treatment decision.

Patients were classified as ‘not for treatment’ if the clinician considered treatment to be inappropriate at diagnosis due to factors such as advanced age, co-morbidity or poor PS.

Treatment, when administered, was given in accordance with the standard protocols for single agent 5-fluorouracil or capcitabine.

### Table 1. Patient treatment categories following a diagnosis of metastatic disease

<table>
<thead>
<tr>
<th>Treatment recommendation</th>
<th>Treatment category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate treatment recommended, patient accepted</td>
<td>Immediate treatment</td>
</tr>
<tr>
<td>Immediate treatment recommended, patient declined</td>
<td>Declined treatment</td>
</tr>
<tr>
<td>Watch and wait approach offered, patient accepted</td>
<td>Watch and wait approach</td>
</tr>
<tr>
<td>Watch and wait approach offered, patient decided to pursue treatment</td>
<td>Immediate treatment</td>
</tr>
<tr>
<td>Not fit for consideration of treatment</td>
<td>Not for treatment</td>
</tr>
</tbody>
</table>

oxaliplatin (given with a fluoropyrimidine) and irinotecan (alone or in combination with a fluoropyrimidine). Body surface area (BSA)-based dosing was used for all patients. Biological agents used included bevacizumab, available for clinical trials before July 2009 and routinely after July 2009. Treatment with epidermal growth factor receptor antibodies (given with second-line irinotecan or as a single agent) was only available for clinical trials during the study period.

Where an initial watch and wait approach was pursued, patient factors at diagnosis, number of active agents ultimately received and overall survival were all explored. This information was compared with patients who received immediate treatment. Patient factors at diagnosis and survival data of the watch and wait patients were also compared with patients who either declined or were unfit for treatment.

Statistical significance was analysed using SAS Enterprise Guide 4.3 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics including median and frequencies were used to describe the study population in each treatment category. The Kaplan–Meier method was used to analyse overall survival.

### results

We identified 758 patients diagnosed with mCRC between January 2003 and December 2010 at participating hospitals. Twenty-two patients (2.9%) were excluded from analysis, including 11 patients with insufficient data collected and 11 patients who, after initial diagnosis and data collection, subsequently received treatment at a non-participating hospital. Ultimately, data on 736 patients (97.1%) were analysed.

#### initial treatment approach

Of the analysed patients, 435 (59.1%) were male and 301 (40.9%) were female. Immediate treatment was received by 377 patients (51.2%). One hundred and ninety-two patients (26.1%) adopted a watch and wait strategy. For 34 patients (4.6%), a recommendation for immediate treatment was declined, predominantly due to concerns regarding toxicity or a preference for non-standard treatments.

Active treatment was not offered to 133 patients (18.1%) at initial diagnosis of metastatic disease due to poor PS ($n=76$, 57.1%), co-morbidity ($n=55$, 41.4%), advanced age ($n=3$, 2.3%) or other reasons ($n=19$, 14.3%). As clinicians were permitted to select multiple reasons, totals add to more than 100%.

Clinical characteristics of the four patient subgroups are summarised in Table 2. Compared with patients undergoing immediate treatment (median age 63.6 years), the median age was higher for all other groups, with this difference being significant for the declined treatment group (median age 74.9 years, $P=0.0001$) and the not for treatment group (median age 77.7 years, $P=0.0001$). The highest proportion of patients with a PS of 0 was seen in the watch and wait group (81.4%), and the lowest (15%) was seen in the not for treatment group.

The percentage of patients with metastatic disease at diagnosis (range 57.9%–72.1%) was similar amongst the patient subgroups. The percentage of patients that received prior adjuvant chemotherapy was numerically highest (21.9%) in those where a watch and wait approach was adopted and
lowest (8.8%) in patients who declined treatment, but differences between the groups were not significant.

**subsequent treatment**

Figure 1 illustrates the cumulative number of patients who have started active treatment at various time points after the initial wait and watch approach was adopted. Of the 192 patients in the watch and wait group, 168 (87.5%) had received chemotherapy at the time of this analysis, with 8 of the untreated patients (33.3%) remaining alive. The median time from diagnosis to commencing treatment was 3.7 months (range 2–35 months).

A chart review of the 24 patients where a watch and wait strategy was employed but chemotherapy was never initiated was conducted. Eleven of these patients had received active treatment in the form of palliative radiotherapy. Of the 16 patients who had died, for 10 cases this was attributed to colorectal cancer and for the remaining 6 other intercurrent illnesses were considered to be the cause of death (as recorded in the death certificate). Of the eight patients who remained alive at the time of analysis, one with ongoing low bulk and asymptomatic disease remained on active surveillance with a plan to initiate chemotherapy at disease progression.

The characteristics of the 168 patients where a watch and wait approach was adopted who later received treatment versus the 24 patients who had not received chemotherapy are shown in Table 3. Treatment was less likely to be initiated at a later date in patients who were older (median age 78.3 years versus 65.5 years, \(P<0.00001\)) and those with an inferior PS > 0 at diagnosis (70.8% versus 48.2%, \(P=0.05\)). The number or sites of metastatic disease had no impact.

Of the 168 patients (86.2%) in the watch and wait group who received treatment, the proportion receiving all active chemotherapy drugs was similar to patients who received immediate treatment at diagnosis (supplementary Table S1, available at Annals of Oncology online).

**patient survival**

Overall survival for the four groups of patients is shown in Figure 2. Poorest outcomes were seen in patients considered, at presentation, not to be fit for treatment (median survival 5 months). For patients who received immediate treatment, the median survival was 17 months. The median survival for the 34 patients who declined to undergo recommended initial therapy was 10 months. The median survival for patients with an initial watch and wait approach was 27 months, significantly better than immediately treated patients (HR 0.68, 95% confidence interval (CI) 0.54–0.85, \(P=0.0008\)).

**discussion**

National Comprehensive Cancer Network (NCCN) guidelines, based on the available evidence, currently recommend active

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**Table 2.** Characteristics of the four patient groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Median age (range)</th>
<th>Eastern Cooperative Oncology Group Performance Status (ECOG PS) = 0 at diagnosis (%)</th>
<th>% of pts with ≥2 sites of distant metastases</th>
<th>% of pts with metastatic disease at initial diagnosis</th>
<th>% of pts with prior adjuvant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate treatment (n = 377)</td>
<td>63.6 (26.2–92.0)</td>
<td>41.3</td>
<td>37.9</td>
<td>72.1</td>
<td>16.2</td>
</tr>
<tr>
<td>Declined treatment (n = 34)</td>
<td>74.9 (44.2–89.1)</td>
<td>38.2</td>
<td>41.2</td>
<td>61.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Watch and wait (n = 192)</td>
<td>66.2 (29.2–95.5)</td>
<td>81.4</td>
<td>29.2</td>
<td>58.9</td>
<td>21.9</td>
</tr>
<tr>
<td>Not for treatment (n = 133)</td>
<td>77.7 (49.3–92.8)</td>
<td>15.0</td>
<td>30.8</td>
<td>57.9</td>
<td>12.0</td>
</tr>
</tbody>
</table>

**Table 3.** Characteristics of the watch and wait group according to whether subsequent chemotherapy treatment was given

<table>
<thead>
<tr>
<th>No. of metastatic sites (%)</th>
<th>Watch and wait—later treatment (n = 168)</th>
<th>Watch and wait—never treated (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years (range)</td>
<td>65.5 (29.2–87.9)</td>
<td>78.3 (43.6–95.5)</td>
</tr>
<tr>
<td>Patients with Eastern</td>
<td>87 (92.6%)</td>
<td>7 (7.4%)</td>
</tr>
<tr>
<td>Cooperative Oncology Group Performance Status (ECOG PS) is equal to 0 at baseline (n = 94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>70.2</td>
<td>70.4</td>
</tr>
<tr>
<td>≥3</td>
<td>25.6</td>
<td>18.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>3.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Sites of metastases (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver only</td>
<td>36.9</td>
<td>20.8</td>
</tr>
<tr>
<td>Lungs only</td>
<td>10.1</td>
<td>16.7</td>
</tr>
<tr>
<td>Lymph node only</td>
<td>6.5</td>
<td>0</td>
</tr>
<tr>
<td>Peritoneum only</td>
<td>7.1</td>
<td>0</td>
</tr>
<tr>
<td>Any including bone</td>
<td>3.6</td>
<td>12.5</td>
</tr>
<tr>
<td>Any including peritoneum</td>
<td>13.7</td>
<td>0</td>
</tr>
<tr>
<td>Multiple or other</td>
<td>29.2</td>
<td>29.2</td>
</tr>
</tbody>
</table>
initial therapy for all patients, tailored according to whether patients are, or are not, appropriate for intensive therapy [4]. Here we demonstrate in a prospective population-based study that a watch and wait approach is frequently employed, that the vast majority of these patients ultimately receive chemotherapy and that such an approach does not appear to compromise survival. The strength of our series is that it was inclusive, and we report data on the treatment and outcomes of virtually all patients (736 of 758, 97.1%) presenting with mCRC at the participating sites.

In summary, of the 736 patients analysed, 377 (51.2%) received immediate treatment, 192 (26.1%) accepted the recommendation of an initial watch and wait approach, 133 (18.1%) were considered too frail for treatment and another 34 (4.6%) patients declined the therapy offered. It is reassuring that the great majority (87.5%) of watch and wait patients subsequently received treatment, at a median of 3.7 months, with a small number of outliers watched for >12 months.

Factors predicting for patients not subsequently receiving treatment were poor PS and advanced age, with the median age of never-treated patients being 13 years older than those that did receive later therapy. This may reflect clinicians being less likely to recommend treatment at progression in older patients, possibly due to increased co-morbidity. The development of significant intercurrent illness was also a factor with six of the deceased patients (25% of the untreated watch and wait patients) having died of another cause other than colorectal cancer. As older patients were more likely to decline treatment at diagnosis (Table 2), it is also possible that some patients simply declined recommended treatment at a later time point despite initially agreeing to a plan for later treatment.

By measures that we were able to analyse, including the number of lines of treatment received and overall survival, there was no evident adverse impact of an initial watch and wait approach. The median survival of the watch and wait group at 27 months is better than we anticipated and superior to the median values typically achieved in recent clinical trials. We feel that this is consistent with the majority of these patients receiving treatment within a few months (median 3.7) of diagnosis, and the overall excellent PS and low bulk disease in these patients. The 17-month median survival of the immediately treated group is consistent with clinical trials in the era before biologic therapy, an appropriate comparator as only a minority of our patients were able to access such therapy. However, in the absence of a prospective randomised study, the true impact, if any, of an initial watch and wait approach on patient survival remains uncertain.

A comparison of the patients in the four treatment groups indicates that patient age was a major factor in determining initial treatment, with the median age of the 133 patients not recommended for treatment being 77.7 years. Notably, however, age alone was the documented dominant reason to not recommend treatment in only three (2.3%) of these patients. This suggests that the co-morbidity and poorer PS that frequently accompanies advancing age are the major contributors to many elderly patients not being treated, and that clinicians are increasingly comfortable with treating patients in their 80s. Indeed (Table 2), patients up to 93 years old were included in the immediately treated group and a 95.5 year old was managed with a watch and wait approach (but ultimately not treated).

One subgroup of patients deserving further investigation is the 34 patients (4.6%) who declined to undergo recommended therapy and this group will be explored in future publications. The older median age suggests that advancing age may diminish patients’ enthusiasm for treatment. However, ignoring medical advice and conventional treatment options may also reflect the modern era, with patients becoming more autonomous and taking increasing responsibility for their health and health-care decisions [6], in parallel with a growing interest in non-standard and complementary therapies.

The potential benefits of a watch and wait approach are several. Chemotherapy treatment is physically and psychologically stressful, can mean time off work and/or missing other commitments, and anything more than a brief vacation whilst on treatment is usually not possible. So patients with asymptomatic disease not undergoing active treatment would be expected to have a better quality of life. We also know that a minority (20%–30%) of patients will have de novo chemorefractory disease and progress through standard treatment. For such patients, ineffective therapy could be delayed or even avoided. Finally, for a minority of actively treated patients intercurrent illness will intervene before the survival benefits of chemotherapy are realised, the likelihood of which will increase with advancing age and/or co-morbidity. Our data do support this as being an important consideration with one quarter of the untreated watch and wait patients ultimately having died of another illness.

The question we were asking is distinct to previous clinical trials, done in the era when 5-fluorouracil was the only available treatment [7, 8], which randomised asymptomatic patients with mCRC to initial chemotherapy versus chemotherapy at symptomatic progression. Many of our immediately treated patients had asymptomatic disease and many of our watch and wait patients would have had treatment initiated before symptomatic progression. In the clinical trials [7, 8], waiting till symptomatic progression meant 30%–40% of patients never received chemotherapy treatment despite this being mandated by the protocol, higher than the percentage in
our series. This does suggest that waiting for symptomatic progression is not the optimal trigger for initiating therapy.

Even if a watch and wait approach is an appropriate strategy, a fundamental question remains as to which patients might benefit from such a strategy, or perhaps more importantly which patients might have their survival compromised by not having immediate treatment. The approach of the oncologists involved in this study seems to have been validated; only utilising a watch and wait approach in patients with low bulk and asymptomatic disease, where patients were considered reliable to attend for regular clinical and radiological assessment and where modest progression was unlikely to lead to significant clinical deterioration that might preclude treatment. Specifically, the latter includes those with peritoneal disease, where even minor degrees of progression may lead to persistent small bowel obstruction and rapid clinical deterioration, making treatment difficult to deliver. As seen in Table 3, peritoneal disease was infrequent in the watch and wait patients, and was not a factor in patients not receiving treatment. Intuitively, patients with metastatic sites known to be associated with a poor prognosis, such as bone metastases, would not be good candidates for a watch and wait approach. Likewise, biomarkers of poor outcome, such as a BRAF mutation [9, 10], also define a group where delayed treatment would be inadvisable.

Reassuringly, our data suggest that very few of the younger and fitter patients missed receiving subsequent therapy (Table 3). Rather, of those managed with a wait and watch approach, it was the older patients and those with a poorer PS who were most likely to never receive chemotherapy, arguably these being the patients where treatment would be less effective and more challenging to deliver safely.

In routine practice, largely driven by the desire to detect potentially resectable liver and lung metastases, the routine use of computed tomography imaging of chest, abdomen and pelvis at the time of diagnosis and intensive surveillance strategies, including regular carcinoembryonic antigen and imaging, will identify an ever increasing number of patients with asymptomatic but incurable disease [11–13]. Therefore, the number of patients where a watch and watch approach could be considered is likely to continually expand, highlighting the relevance of the data presented here. We conclude from our series that an initial watch and wait approach, with careful follow-up and initiation of treatment at an appropriate time, is a valid strategy in selected patients. Not all clinicians will be comfortable with this approach, and we would advocate for additional studies that further inform this discussion, and provide added reassurance to both clinicians and patients.

disclosure

The authors have declared no conflict of interest.

references