

# Chemotherapy for Advanced Colorectal Cancer among Indonesians in a Private Hospital in Jakarta: Survival when Best Treatment is Given

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## ABSTRACT

**Background:** Survival of colorectal cancer in Indonesia is thought to be shorter due to several factors, among these: ethnic, nutritional, and the low affordability factors. Aim of this study to assess and evaluate survival in advanced colorectal cancer when given the best drugs available as recommended by international guidelines.

**Method:** A historical cohort study was done in patients with advanced colon or rectal cancer between 2008 and 2010 at Medistra Hospital. Cases were retrieved from medical record data. Subjects were included if they were diagnosed or had a relapse of their disease during the study period and were followed until they died or lost to follow-up. Staging procedure was done using the tumor node metastasis (TNM) system. All patients received the combination of 5-fluorouracil (5-FU)/leucovorin (LV), oxaliplatin for 6 cycles (FOLFOX4) as the standard first-line regimen for metastatic colorectal cancer (mCRC) in Indonesia. Oral capecitabine and targeted therapy such as bevacizumab and cetuximab might were also given, whenever indicated.

**Results:** Nineteen patients (48.7%) died during the study period, while the rest were alive or lost to follow-up. The median overall survival of patients was 18 months (95% CI = 6.98 – 29.02 months). The longest survival was 76 months (the patient is still alive when this manuscript was being prepared). Patients with colon cancer tended to live longer than rectal cancer, i.e. 21 vs. 15 months; log-rank  $p = 0.147$ . There was no significant difference of survival between patients with stage IV disease and relapse cases, i.e. 18 vs. 12 months, log-rank  $p = 0.807$ .

**Conclusion:** With proper treatment and access to cytostatics and biologicals, advanced colorectal cancer among Indonesian patients have the same survival rates as patients in more developed countries as reported in the literature.

**Keywords:** advanced colorectal cancer, chemotherapy, survival

## ABSTRAK

**Latar belakang:** Kesintasan kanker kolorektal di Indonesia agaknya lebih singkat karena beberapa faktor, di antaranya adalah suku, gizi dan kemampuan yang rendah. Tujuan penelitian ini adalah untuk mengkaji dan menilai kesintasan kanker kolorektal tahap lanjut ketika pasien diberikan obat-obat terbaik yang tersedia di pasaran sebagaimana disarankan oleh pedoman internasional.

**Metode:** Penelitian kohort retrospektif dilakukan pada pasien dengan kanker kolon atau kanker rektum tahap lanjut antara tahun 2008 dan 2010 di Rumah Sakit Medistra. Kasus didapatkan berdasarkan data rekam medik. Subyek penelitian diikutsertakan bila pasien didiagnosis atau menderita relaps penyakit selama periode penelitian dan diikuti hingga mereka meninggal atau hilang untuk ditindaklanjuti. Prosedur penetapan stadium kanker dilakukan dengan menggunakan sistem tumor node metastasis (TNM). Semua pasien mendapatkan kombinasi 5 fluorourasil (5-FU)/leukovorin (LV), oksaliplatin selama 6 siklus (FOLFOX4) sebagai regimen lini pertama standar untuk metastasis kanker kolorektal di Indonesia. Kapesitabin oral dan terapi target seperti bevakizumab dan setuksimab juga diberikan, bilamana diperlukan.

**Hasil:** Sembilan belas pasien (48,7%) meninggal dunia selama periode penelitian, selebihnya masih hidup atau tidak dapat ditindaklanjuti. Nilai median dari kesintasan hidup pasien secara keseluruhan adalah 18 bulan (95% CI = 6,98 – 29,02 bulan). Kesintasan hidup terlama adalah 76 bulan (pasien masih hidup ketika manuskrip ini disiapkan). Pasien dengan kanker kolon cenderung hidup lebih lama daripada kanker rektum, yakni 21 bulan dibandingkan 15 bulan; nilai  $p$  log-rank = 0,147). Tidak ada perbedaan yang bermakna dalam hal kesintasan antara pasien dengan penyakit stadium IV dan kasus-kasus relaps, yakni 18 bulan dibandingkan 12 bulan dengan nilai  $p$  log-rank = 0,807.

**Simpulan:** Dengan pengobatan yang tepat dan akses menuju obat-obat sitostatik dan biologik, kanker kolorektal tahap lanjut pada pasien-pasien di Indonesia mempunyai tingkat kesintasan hidup yang sama dengan pasien-pasien di negara yang lebih maju sebagaimana yang dilaporkan dalam kepustakaan.

**Kata kunci:** kanker kolorektal tahap lanjut, kemoterapi, kesintasan

## INTRODUCTION

Colorectal cancer is the fourth most common cancer in Indonesia with an estimated age-standardized incidence of 17.2 per 100,000 populations for both sexes.<sup>1</sup> About 20% of patients present with distant metastasis, conferring a 11.9%, 5-year relative survival in some reports.<sup>2,3</sup> In another report cancer registry in Indonesia is still being developed, but data from a private hospital in Jakarta (unpublished) revealed that 34% of colorectal patients presented at a metastatic stage. In many instances, patients with metastatic colorectal cancer (mCRC) in Indonesia often do not receive adequate treatment because of the prohibitive cost of treatment and the perception – from doctors and patients alike - that the effort is futile and that the patient will not live longer despite the high cost treatment.

For many decades, 5-fluorouracil (5-FU) has been the mainstay of treatment for mCRC with a very short survival. The addition of oxaliplatin to 5-FU has improved overall survival and response rate compared with 5-FU alone.<sup>4,5</sup> Currently, the combination of multiple agents with 5-FU, leucovorin (LV) and oxaliplatin (FOLFOX) has been the standard regimen for first line chemotherapy for metastatic CRC.<sup>6</sup> This regimen has prolonged median survival to about 20 months in patients with mCRC.<sup>7,8</sup> In recent years, FOLFOX plus bevacizumab as a second-line therapy in patients who previously has been treated with 5-FU/LV and irinotecan (FOLFIRI) showed a median survival of 10.7 months,<sup>9</sup> thus ushering the era of “biological” as part of the systemic treatment armamentarium for colorectal cancer, notably for stage IV.

An important factor that has been mentioned in the literature is the different outcomes of treatment, with the tenet “A drug which work for one patient may not work in another patient with the same cancer” in

which not just ethnicity or race but socioeconomic status is a factor, an observation reported even in the United States.<sup>10</sup> The analogy is not missed in the Indonesian population where, with the wide spectrum of affordability and access to the best medical care, different outcomes are to be expected. Although the benefit of combination chemotherapies has been established elsewhere, less is known in developing countries, including Indonesia. No study has been conducted in Indonesia addressing the efficacy of multi cytotoxic agents on the patient’s survival for those who can afford the best treatment. The aim of this study is to evaluate the survival of metastatic colorectal cancer in the patients, and a good source of study would be a private hospital.

## METHOD

This is a historical cohort study of patients with advanced colon or rectal cancer between 2008 and 2010 in Medistra Hospital. Cases were retrieved from medical record data. Subjects were included if they was diagnosed or had a relapse disease during the study period and were followed until they died or the last follow-up. Patients with no record of any kind of treatment or other primary cancer were excluded from the analysis.

Diagnosis of colon or rectal cancer was established histopathologically, either using a biopsy or surgical specimen. Staging procedure was done using the TNM system. Metastatic disease was evaluated clinically supported by imaging studies such as chest X-ray, abdominal ultrasound, abdominal or head computed tomography (CT) scanning, magnetic resonance imaging, and bone scan. Stage IV disease was defined as the evidence of any distant malignant process at diagnosis. Relapse disease was defined as the evidence of any distant recurrence with or without loco regional

recurrence after primary treatment has been completed without evidence of any clinical residual disease.

Patients' demographics were presented descriptively. Overall survival was calculated from the date of diagnosis for stage IV group or the date of relapse diagnosis for relapsed group until the patient died or the last date of follow-up. Overall survival was analyzed using the Kaplan-Meier curve and log-rank test. A p value of less than 0.05 was considered significant. Data were analyzed using the statistical software SPSS for Windows version 11.5 (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

There were 104 patients with colorectal cancer during the study period; 22 (21.2%) of them present with stage IV disease and 17 (16.3%) other were relapsed patients giving a total of 39 mCRC cases as the study subjects. Their mean age was  $57.4 \pm 13.3$  years, ranging from 30 to 84 years old. The peak age was between 51 and 60 years. Liver and lung were the predominant sites of metastasis, which were found in 28 (71.8%) and 17 (43.6%) patients, respectively. Twenty-five (64.1%) patients presented with colon cancer (Table 1). Adenocarcinoma was

the only histopathology found in these cases. Three patients were excluded from the analysis due refusal to treatment, returning to home country (Japan), and having other primary cancer (malignant mixed Müllerian cancer of the ovary).

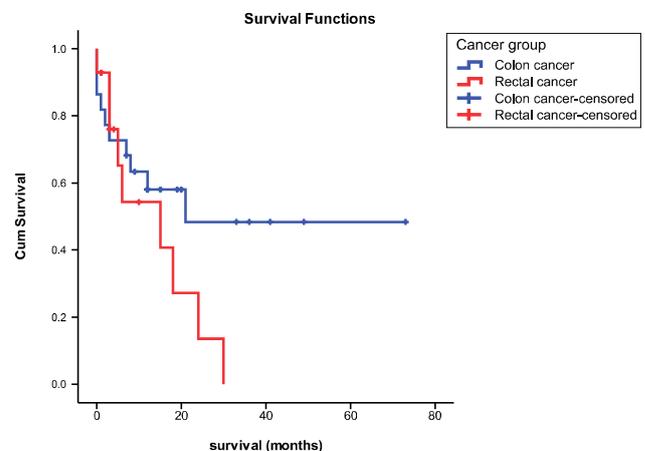
All patients received the combination of 5-fluorouracil (5-FU)/leucovorin (LV), oxaloplatin for 4 cycles (FOLFOX4) as the standard first-line regimen for mCRC in Indonesia. Oral capecitabine and targeted therapy such as bevacizumab and cetuximab were also given, whenever indicated. Some patients may need additional treatment, such as palliative hepatic resection and radiotherapy for pain alleviation.

Nineteen (48.7%) patients died during the study period, while the rest were alive or lost of follow-up. The median overall survival of patients was 18 months (95% CI = 6.98–29.02 months). The longest survival was 76 months (the patient is still alive when this manuscript was being prepared). Patients with colon cancer tended to live longer than rectal cancer, i.e. 21 vs. 15 months; log-rank  $p = 0.147$  (Figure 1). There was no significant difference of survival between patients with stage IV disease and relapse cases, i.e. 18 vs. 12 months, log-rank  $p = 0.807$  (Figure 2).

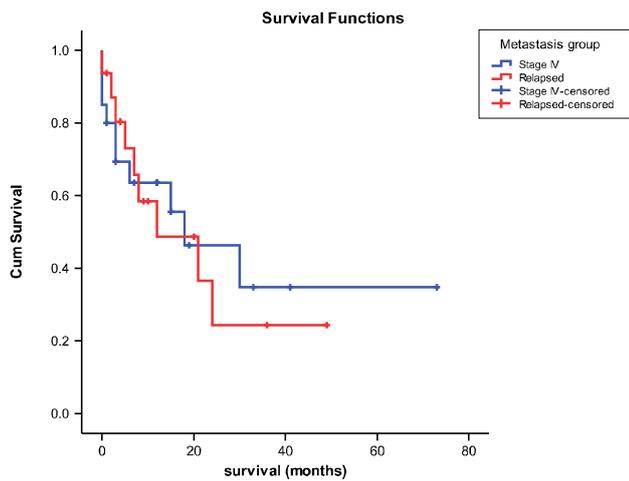
The median survival of patients who received FOLFOX (with or without oral capecitabine or targeted therapy) has not been reached at the time of the preparation of this article, while patients who did not receive FOLFOX regimen had a median survival of 12 months. This difference was statistically significant (Figure 3). Furthermore, 5 of 15 (33%) patients who received FOLFOX had survival more than 2 years.

**Table 1. Characteristics of the study subjects (n = 39)**

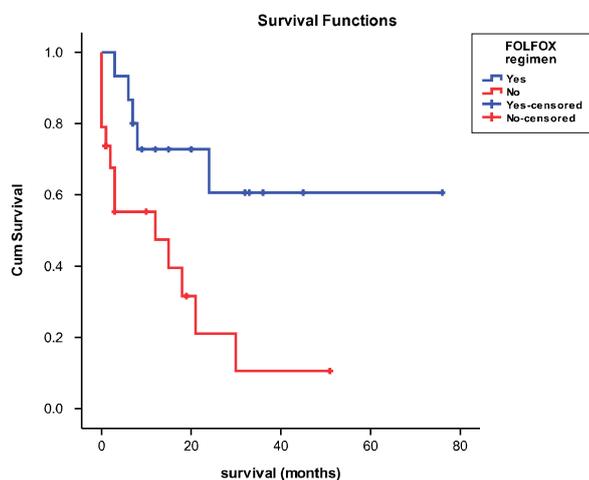
Variable	n (%)
Sex	
Male	21 (53.8)
Female	18 (46.2)
Age group (years)	
21 – 30	1 (2.6)
31 – 40	3 (7.7)
41 – 50	8 (20.5)
51 – 60	12 (30.8)
71 – 80	3 (7.7)
> 80	3 (7.7)
Location	
Colon	25 (64.1)
Rectum or rectosigmoid	14 (35.9)
Site of metastasis	
Liver only	14 (35.9)
Liver and lung	9 (23.1)
Lung only	4 (10.3)
Liver and bone	2 (5.1)
Ovary	1 (2.6)
Pancreas	1 (2.6)
Liver and ovary	1 (2.6)
Lung and bone	1 (2.6)
Lung and ovary	1 (2.6)
Bone and kidney	1 (2.6)
Intestinal wall	1 (2.6)
Liver, lung and brain	1 (2.6)
Liver, lung and kidney	1 (2.6)
Liver, kidney and bladder	1 (2.6)



**Figure 1. Kaplan-Meier survival curve analyses of patients with colon or rectal cancer. The difference was not statistically significant (log-rank  $p = 0.147$ )**



**Figure 2. Kaplan-Meier survival curve analyses of patients with stage IV or relapsed diseases. The difference was not statistically significant (log-rank  $p = 0.807$ )**



**Figure 3. Kaplan-Meier survival curve analyses of patients who received FOLFOX chemotherapy or not. The difference was statistically significant (log-rank  $p = 0.01$ )**

**DISCUSSION**

The ongoing research into the characteristic of cancer and recent advances in the treatment of metastatic colorectal cancer have resulted in change in outlook and the decision-making of the clinician to be ever more complex, such that the endeavour to prolong survival will have to take into consideration on quality of life. The advent of newer drugs, regimens, and the use of targeted therapies - mostly the monoclonal antibodies – mCRC has subsequently become a chronic disease with a median overall survival (mOS) of more than 2 years and a 5-year survival of 10% (previous figures stated as 5%).

This is the first clinical study in in Indonesia evaluating mCRC in hospital setting since the introduction of FOLFOX regimen. Cases were

intentionally selected from a private hospital because financially they can afford chemotherapy regimen. Our results confirmed the benefit of oxaliplatin. Median survival of 18 months were comparable with other studies. The survival benefit was seen either in stage IV patients or relapse cases. This observation emphasize the importance of adequate treatment of patients with metastatic disease, regardless prior stage.

FOLFOX regimen given for four cycles continuously (FOLFOX4) has been routinely used as the first-line option for mCRC in Indonesia. However, OPTIMOX1 trial suggested that physicians may opt to stop high-dose oxaliplatin after 6 cycles, followed by infusional FU/LV and then reintroduce oxaliplatin again (“stop-and-go”).<sup>11</sup> This approach was introduce after recognizing that the majority of patients treated with continues FOLFOX will discontinue for neurotoxicity before progression.

In further trials addressing complete discontinuation of treatment, the OPTIMOX2 trial failed to show clear benefit and suggested that chemotherapy should not be discontinued.<sup>12</sup> To achieve prolonged survival, a complete stop of all therapy is not the correct strategy.<sup>13</sup> This applies not only to chemotherapy but other treatment modalities as well, as palliative surgery and radiotherapy Study showed that median survivas may exceed 30 months and more patients could live up to 4 and 5 years with advanced disease after hepatic resection and improved chemotherapy.<sup>14</sup>

Multiple cytotoxic agents and targeted therapy has been accepted as the standard treatment for mCRC. Instead of giving treatment sequentially as the disease progress, a more continuous approach has been suggested, whereby individualization of care is offered before it happens, the so-called ‘continuum of care’.<sup>15</sup> However, at the end of the day, the role of biologicals (popularly known as “targeted therapy”) have been modest at best, as they have not been shown to be active in the adjuvant setting – the most important phase of chemotherapy in colorectal cancer.<sup>17</sup>

There was a limitation in this study which warrants further improvement in documentation, as clinical factors were not included. A cohort prospective design would be a preferable method for survival study; however, without a proper baseline data, such study would be difficult to plan and too expensive, but this current study would serve as a platform for further clinical research on treatment of advanced colorectal in Indonesia.

To be fair, suffice it to say that the conditions in Indonesia, though in varying degrees – is not unique. Improvement in survival has been acknowledged with the

use of more and better drugs. Yet we find that the benefits of treatment have not been satisfactory as they have not touched the whole population, especially for the elderly.<sup>18</sup>

After the results of the N9741 Trial was announced,<sup>19</sup> in which 5-year survival of the FOLFOX regimen was shown to be higher than irinotecan plus fluorouracil and leucovorin (IFL), the *overall survival* (OS) and *time to progression* (TTP) 20.2 months and 8.9 months, respectively, chemotherapy for colorectal cancer has not moved back ever since. Following in the footsteps and in mCRC, the use of “targeted therapy” or biologicals – as it is now more commonly known – a more personalized approach, started by the use of KRAS testing as a marker, has been regarded as the direction in the last decade.<sup>20</sup> The benefits of targeted therapy itself were earlier reported in 2009 by Chau with the use of bevacizumab,<sup>21</sup> in which its use was reported to improve efficacy (over the use of cytostatics alone) both as first and second-line treatment. But it was the KRAS test which forged the importance of markers. In our series, the use of KRAS has been minimal at best, mostly due to technical difficulties and cost. This has been the reason that bevacizumab was more utilized in our patients.

The road to the “perfect treatment”, for Indonesians and the rest of the world in that matter, is a long way off. Much has been accomplished, although the last decade did not meet expectations for the targeted therapies,<sup>22</sup> and the answer may lie perhaps with cellular phenotyping,<sup>22</sup> correlated with chemotherapy regimens and response to therapy, which for all practicality is a distant horizon.

## CONCLUSION

Patients with metastatic colorectal cancer have a modest survival with a median of 18 months. In our study, the chance to live longer was comparable between stage IV and relapsed patients. Chemotherapy combination with FOLFOX significantly prolongs survival, with about one-third of patients live longer than 2 years, a figure not unlike reported in the literature. We conclude that, with proper treatment and care, Indonesian colorectal cancer patients have the same survival as in developed countries.

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