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Estimation of an optimal chemotherapy utilisation rate for colon cancer: An evidence-based benchmark for cancer care

Susannah Jacob[a,*], *Weng Ng*[a], *Ray Asghari*[b], *Geoff P. Delaney*[a], *Michael B. Barton*[a]

[a]*Collaboration for Cancer Outcomes Research and Evaluation (CCORE), Liverpool Hospital, Locked Bag 7103, Liverpool BC, NSW 1871, Sydney, Australia*
[b]*Bankstown Hospital, Sydney, Australia*

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ABSTRACT

Background: Optimal chemotherapy (CT) utilisation rates can serve as benchmarks to assess the quality of cancer care. This study aims to determine the optimal proportion of patients with colon cancer that should receive chemotherapy at least once.
Methods: An optimal chemotherapy utilisation tree was constructed using indications for chemotherapy identified from evidence-based treatment guidelines. Data on the proportion of patient and tumour-related attributes for which chemotherapy was indicated were obtained and merged with the treatment indications to calculate an optimal chemotherapy utilisation rate (CTU rate). This optimal rate was compared with reported actual rates of chemotherapy utilisation.
Results: Chemotherapy is indicated at least once in 55% of patients with colon cancer. While 89% of colon cancer patients presenting with Stage IV disease should optimally receive chemotherapy, 38–52% actually received chemotherapy as part of their initial treatment.
Conclusion: The optimal chemotherapy utilisation rate can serve as an evidence-based benchmark in the planning and evaluation of chemotherapy services. Chemotherapy may be under-utilised in the initial management of patients presenting with metastatic colon cancer.

1. Introduction

Chemotherapy (CT) can improve both the survival and the quality of life of patients with colon cancer.[1–4] Published chemotherapy utilisation rates (CTU rates) for colorectal cancer range from 20% to 35% internationally.[5–8] No benchmark rate of utilisation exists against which these reported chemotherapy utilisation rates can be compared.

This study aims to estimate the optimal proportion of patients with colon cancer that should receive chemotherapy at least once, based on the best available evidence. This optimal chemotherapy utilisation rate can serve as a benchmark to assist in the planning and delivery of chemotherapy services. This study was part of a larger project to estimate an optimal chemotherapy utilisation rate for all cancers.

2. Materials and methods

2.1. *Indications for chemotherapy*

An indication for chemotherapy was defined as a clinical situation in which chemotherapy is the treatment of choice on the basis of superior clinical outcomes in comparison to other treatment modalities (including best supportive care or no

* *Corresponding author:* Tel.: +61 2 9828 6542; fax: +61 2 9828 6670.
E-mail address: Susannah.Jacob@sswahs.nsw.gov.au (S. Jacob).
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treatment). The superiority of chemotherapy over other treatment options could be based on survival, quality of life or toxicity profile. Chemotherapy could be recommended either alone or in combination with radiotherapy (RT) or surgery.

The lists of drugs classified as chemotherapeutic agents were as defined in the SEER*RX Interactive Antineoplastic Drug Database of the National Cancer Institute.[9] The optimal choice of individual drugs or chemotherapy regimens was beyond the scope of this study.

The evidence-based indications for chemotherapy in colon cancer were identified from published international clinical practice guidelines[10–19] (see Table 1). The evidence in support of each indication for chemotherapy was ranked according to the National Health and Medical Research Council's (NHMRC's) hierarchy of levels of evidence.[20]

2.2. *Incidence data (tumour and patient attributes)*

Data on the proportion of tumour and patient attributes for which chemotherapy is indicated were identified and ranked using a previously described hierarchy[21–28] (see Table 2). In situations where data on an attribute were available from multiple sources, the data ranked highest quality were used as the base value in the chemotherapy utilisation tree.

2.3. *Performance status*

Performance status (PS) is a major prognostic factor used to select patients eligible for chemotherapy. No specific population-based performance status data could be identified for patients with colon cancer. We therefore estimated the proportion of age-adjusted good performance status patients by combining Australian national data on age incidence of colon cancer with population-based data on the degree of difficulty experienced in undertaking daily work or activities (this correlates with the Eastern Cooperative Oncology Group (ECOG) scoring scales) in each of the corresponding age groups.[29,30] The estimates of performance status were age-adjusted because the incidence and proportion of good performance status patients vary with age.

Table 1 – Colon cancer: Indications for chemotherapy – levels and sources of evidence.

Outcome number	Clinical scenario in which chemotherapy is indicated	Level of evidence*	References	Proportion of all colon cancer patients
3	ECOG 0–2, Stage I, surgery, recurrence, resectable hepatic metastases	II	NCCN,[10] NHMRC,[11] NICE[13]	<0.01
4	ECOG 0–2, Stage I, surgery, recurrence, non-resectable hepatic metastases	I	NHMRC,[11] NCCN,[10] NICE,[13] SIGN,[12] Cochrane,[14] BCCA[15]	<0.01
5	ECOG 0–2, Stage I, surgery, recurrence, other metastases	I	NHMRC,[11] NCCN,[10] NICE,[13] SIGN,[12] Cochrane,[14] BCCA[15]	0.01
6	ECOG 0–2, Stage II, surgery, 'high-risk' of recurrence	II	NCCN,[10] ASCO,[16] NHMRC,[11] NICE,[13] CCOPGI,[17] BCCA[15]	0.07
9	ECOG 0–2, Stage II, 'low-risk', surgery, recurrence, resectable hepatic metastases	II	NCCN,[10] NHMRC,[11] NICE[13]	<0.01
10	ECOG 0–2, Stage II, 'low-risk', surgery, recurrence, non-resectable hepatic metastases	I	NHMRC,[11] NCCN,[10] NICE,[13] SIGN,[12] Cochrane,[14] BCCA[15]	0.01
11	ECOG 0–2, Stage II, 'low-risk', surgery, recurrence, other metastases	I	NHMRC,[11] NCCN,[10] NICE,[13] SIGN,[12] Cochrane,[14] BCCA[15]	0.03
12	ECOG 0-2, Stage III	I	NHMRC,[11] NCCN,[10] BCCA,[15] CCOPGI,[18] SIGN,[12] NICE,[13] NCI[19]	0.25
13	ECOG 0–2, Stage IV, resectable hepatic metastases	II	NCCN,[10] NHMRC,[11] NICE[13]	<0.01
14	ECOG 0–2, Stage IV, non-resectable hepatic metastases	I	NHMRC,[11] NCCN,[10] NICE,[13] SIGN,[12] Cochrane,[14] BCCA[15]	0.05
15	ECOG 0–2, Stage IV, other metastases	I	NHMRC,[11] NCCN,[10] NICE,[13] SIGN,[12] Cochrane,[14] BCCA[15]	0.12
The total proportion of patients with colon cancer in whom chemotherapy is recommended				0.55 (55%)

Abbreviations: PS – performance status, ECOG – Eastern Cooperative Oncology Group, NHMRC – National Health and Medical Research Council (Australia), NCCN – National Comprehensive Cancer Network (USA), NCI PDQ – National Cancer Institute Physicians Data Query (USA), ASCO – American Society of Clinical Oncologists, CCO – Cancer Care Ontario, BCCA – BC Cancer Agency.

* *Levels of Evidence for Indications for Chemotherapy:* Level I – evidence obtained from a systematic review of all relevant randomised controlled trials; Level II – evidence obtained from at least one properly designed randomised controlled trial; Level III – evidence obtained from well-designed controlled trials without randomisation -these include trials with 'pseudo-randomisation' where a flawed randomisation method was used (e.g. alternate allocation of treatments) or comparative studies with either comparative or historical controls; Level IV – evidence obtained from case series. Taken from the National Health and Medical Research Council (NHMRC) hierarchy of levels of evidence.[20]

Table 2 – Colon Cancer: The incidence of attributes used to define indications for chemotherapy.

Key	Population or subpopulation of interest	Attribute	Proportion of populations with this attribute	Quality of information	References
A	All registry cancers	Colon cancer	0.097	α	AIHW 2003[22]
B	All Colon Cancer	Good performance status (ECOG 0-2)	0.89	α δ	AIHW 2003[22] NSW Population Health Survey *[23]
C	All Colon Cancer	Stage I (T1-2N0M0)	0.22	α	National colorectal cancer survey[7]
D	Stage I (T1-2N0M0), surgery	Recurrence	0.05	ε	SWS colorectal cancer database
E	Stage I (T1-2N0M0), surgery, recurrence	Isolated local recurrence	0.11	λ	Willett et al.[24]
F	Stage I (T1-2N0M0), surgery, recurrence	Hepatic only metastases	0.22	λ	Willett et al.[24]
G	Stage I (T1-2N0M0), surgery, recurrence, only hepatic metastases	Resectable hepatic metastases	0.20	γ	Manfredi et al.[25]
H	All Colon Cancer	Stage II (T3-4N0M0)	0.30	α	National colorectal cancer survey[7]
I	Stage II (T3-4N0M0)	High risk	0.28 0.18	β ε	Morris et al.[26] Gill et al.[36]
J	Stage II (T3-4N0M0), low risk	Recurrence	0.28	λ	Willett et al.[24]
K	Stage II (T3-4N0M0), low risk, recurrence	Isolated local recurrence	0.21	λ	Willett et al.[24]
L	Stage II (T3-4N0M0), low risk, recurrence	Hepatic only metastases	0.21	λ	Willett et al.[24]
M	Stage II (T3-4N0M0), low risk, recurrence, hepatic metastases	Resectable metachronous hepatic metastases	0.20	γ	Manfredi et al.[25]
N	All colon cancer	Stage III (TxN1-2M0)	0.28	α	National colorectal cancer survey[7]
O	All colon cancer	Stage IV (TxNxM1)	0.20	α	National colorectal cancer survey[7]
P	Stage IV (TxNxM1)	Metastases confined to liver only	0.45 0.32	δ θ	Kune et al.[27] Russell et al.[28]
Q	Stage IV, hepatic metastases	Resectable synchronous hepatic metastases	0.07	γ	Manfredi et al.[5]

Abbreviations: PS – performance status, ECOG – Eastern Cooperative Oncology Group, RT – radiotherapy, AIHW – Australian Institute of Health and Welfare, SWS – South Western Sydney.

Hierarchy for epidemiological data[21]: α – Australian National Epidemiological data; β – Australian State Cancer Registry; γ – epidemiological databases from other large international groups (e.g. SEER); δ – results from the reports of a random sample from a population; ε – comprehensive multi-institutional database; ζ – comprehensive single-institutional database; θ – multi-institutional reports on selected groups (e.g. multi-institutional clinical trials; λ – single-institutional reports on selected groups of cases; μ – expert opinion.

* Performance status data are estimated from the general population and are not specific to colon cancer patients.

2.4. *Optimal chemotherapy utilisation rate*

The indications for chemotherapy treatment in Table 1 and the incidence data on the proportion of tumour and patient attributes in Table 2 were merged to generate an optimal chemotherapy utilisation tree for colon cancer using TreeAge Pro 2007 software. Each branch of the chemotherapy utilisation tree represents an important tumour or patient-related attribute that affects whether chemotherapy is indicated.

In the tree, each patient with an indication for chemotherapy treatment was only counted once (i.e. the tree was terminated at the point of chemotherapy being recommended) even if they developed subsequent indications for chemotherapy later during the course of their illness. The optimal utilisation rate was calculated from the summation of the incidence of each indication for chemotherapy. This was then compared with actual chemotherapy utilisation rates reported in the literature.

The utilisation tree was externally reviewed by independent experts from the Australasian Gastrointestinal Trials Group, New South Wales Oncology Group and Victoria Cooperative Oncology Group to ensure clinical validity.

3. Results

Fig. 1 shows the optimal chemotherapy utilisation tree for colon cancer.

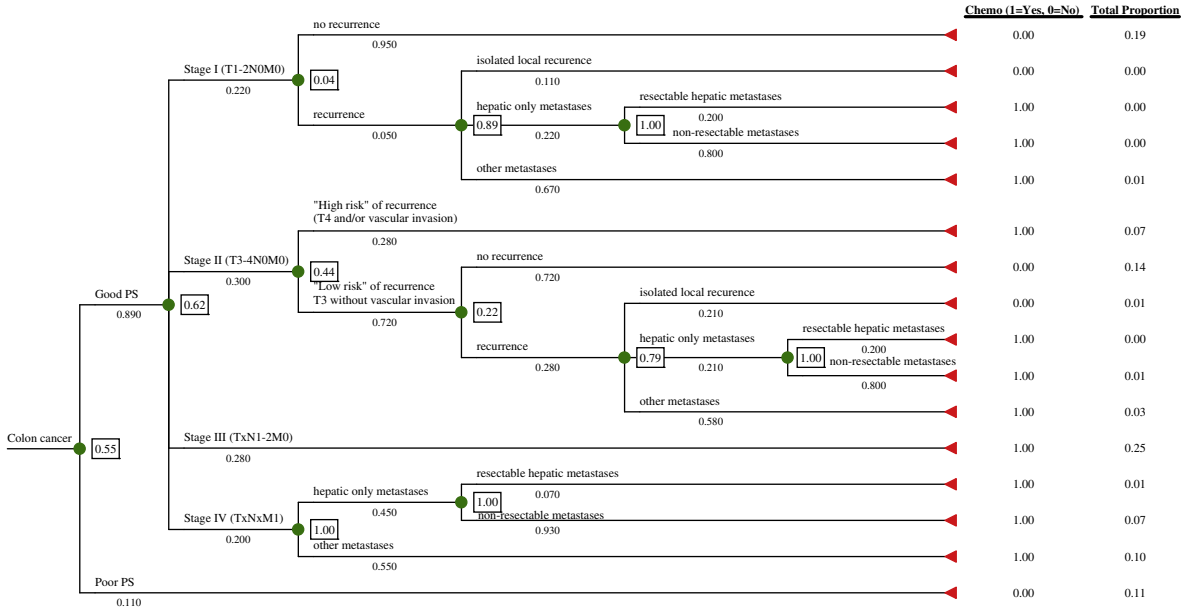

Fig. 1 – Optimal chemotherapy utilisation tree for colon cancer.

Chemotherapy is indicated at least once, according to the best available evidence, in 55% of patients with colon cancer.

3.1. *Sensitivity analysis*

Sensitivity analysis was used to assess the extent to which the optimal chemotherapy utilisation rate was affected by uncertainty in the indications for chemotherapy or in the epidemiological data.

Whether chemotherapy is indicated for patients with Stage II colon cancer is controversial and hence sensitivity analysis was conducted. In our model, only patients with 'high-risk' Stage II colon cancer are recommended to receive chemotherapy. If chemotherapy were not recommended for any patients with Stage II colon cancer, then the utilisation rate for colon cancer would fall from 55% to 49.5% (see Fig. 2).

There is varied opinion regarding whether adjuvant chemotherapy is indicated following surgery for resected hepatic metastases from colon cancer. However this has no effect on the overall optimal chemotherapy utilisation rate for colon cancer because the proportion of patients involved was very small.

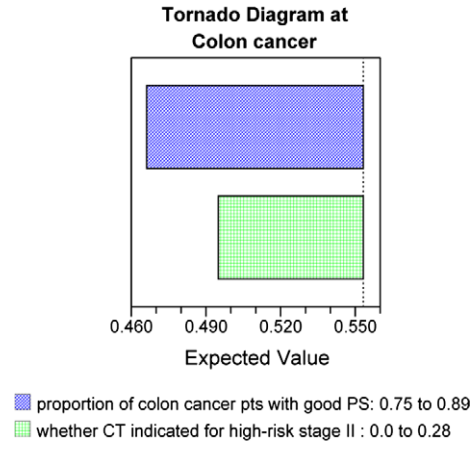

Fig. 2 – Tornado analysis of the variation in data and uncertainty in indication for chemotherapy for colon cancer.

The proportion of patients with colon cancer who have 'good' performance status (ECOG 0–2) was uncertain, ranging from 75% to 90% of all patients. The uncertainty in performance status data varied the chemotherapy utilisation rate for colon cancer from 47% to 55% as shown in the tornado diagram below (see Fig. 2).

3.2. *Optimal versus actual chemotherapy utilisation*

We compared the optimal chemotherapy utilisation rates for colon cancer with reported initial treatment data[7,8,31,32] (Table 3). Both the optimal and the actual utilisation rates in Table 3 represent initial management only.

Table 3 shows that some patients presenting with Stage I colon cancer received chemotherapy as part of their initial treatment, against guideline recommendations. A shortfall in chemotherapy utilisation is seen among patients presenting in Stage IV.

Table 4 shows that chemotherapy utilisation rates for Stage III colon cancer fall with increasing age; data from the National Cancer DataBase show that in 2006 around a quarter of Stage III colon cancer patients aged 80 and over received chemotherapy.[31]

4. Discussion

We calculated that chemotherapy is indicated at least once, according to the best available evidence, in 55% of all patients with colon cancer. The methodology used in this study is easily reproducible and can be applied to any population, taking into account factors such as the relative stage proportions in colon cancer which may vary according to the screening rates in the population. The optimal chemotherapy utilisation tree

Table 3 – Colon cancer: comparison of optimal chemotherapy utilisation rate with actual chemotherapy utilisation rates.

Stage	Optimal chemotherapy utilisation rate (%)		Actual chemotherapy utilisation rates (initial treatment) (%)					
			Australia (2000)[7]		NSW (2000)[8]		USA (2000)[32]	USA (2006)[31]
	At any time	Initial treatment	Offered CT	Received CT	Offered CT	Received CT	Received CT	Received CT
I	4	0	6	3	5	2	*	1.5
II	40	25	29	15	27	17	34	18
III	89	89	76	64	75	59	66	54
IV	89	89	67	49	70	52	*	51
All stages	55	50	44	32	43	31	*	28

* No information available, CT – chemotherapy.

Table 4 – Chemotherapy utilisation by age for Stage III colon cancer patients.

Age	USA 2006[31]			Australia 2000[7]			NSW 2000[8]		
	No. of cases	No. given CT	CTU rate (%)	No. of cases	No. given CT	CTU rate (%)	No. of cases	No. given CT	CTU rate (%)
0–49	1534	1121	73	43	35	81	109	92	84
50–59	2594	1817	70	101	83	82			
60–69	3478	2335	67	159	121	76	126	93	74
70–79	4305	2350	55	175	92	53	147	72	49
80+	3858	953	25	94	15	16	86	17	20

Abbreviations: CT – chemotherapy; CTU rate – chemotherapy utilisation rate.

can also be adapted to take into account any future changes in chemotherapy indications.

Comparisons of the calculated optimal utilisation rate with reported actual rates (Table 3) show that a significant proportion of eligible patients presenting with metastatic colon cancer do not receive chemotherapy. One of the possible reasons for this may be refusal of treatment by patients. The Australian National Colorectal Cancer Survey reports that 18% of Stage IV colon cancer patients who were offered chemotherapy did not receive chemotherapy.[7] Table 3 shows that a significant proportion of Australian colon cancer patients in all stages who were offered chemotherapy did not take it up. Another study of colorectal cancer patients found that the majority were willing to gamble mortality or trade longevity to undergo surgical resection only and avoid chemotherapy.[33] Further research is indicated into the reasons why patients refuse chemotherapy, and whether this changes over time.

The NICE colorectal cancer guidelines state that 'fitness to receive chemotherapy should be made on the basis of performance status and co-morbidity, rather than age'.[13] Analysis of data from randomised trials of both adjuvant and palliative chemotherapy have found that elderly patients with colorectal cancer (admittedly only those who were fit enough to be entered into randomised trials) receive the same benefit from chemotherapy as younger patients.[34–36] Therefore in the optimal chemotherapy utilisation trees, performance status (but not age) is considered as a key factor that affects whether or not chemotherapy is recommended for colon cancer. In practice however, reduced chemotherapy utilisation and referral rates in older patients with colorectal cancer have been reported from several countries and this is also demonstrated in Table 4.[32,37,38]

Some indications for chemotherapy are not explicitly recommended by the guidelines because the evidence is inconclusive. The evidence in favour of adjuvant chemotherapy in Stage II colon cancer is inconclusive, with the results from meta-analyses indicating no significant survival benefit for adjuvant chemotherapy for Stage II colon cancer.[36,39,40] The QUASAR trial showed that chemotherapy improved survival but the absolute improvement in survival in unselected Stage II colorectal cancer was small.[3] In the optimal chemotherapy utilisation tree, adjuvant chemotherapy is indicated only for patients with Stage II colon cancer who have high-risk features. The optimal chemotherapy utilisation rate in colon cancer falls from 55% to 49% if chemotherapy is not indicated for any Stage II colon cancer patients. If in the future further evidence in favour of chemotherapy for all Stage II colon cancer patients were to be published, then the optimal chemotherapy utilisation rate would rise to 70% if all Stage II patients were treated.

The strengths of this model include the use of evidence-based treatment guidelines to develop indications for chemotherapy in colon cancer. The complexities of clinical (e.g. performance status) and pathological factors (e.g. stage) that may affect chemotherapy use in clinical practice were included in the model. In situations where the evidence in favour of chemotherapy is inconclusive (e.g. in Stage II colon cancer), sensitivity analysis was conducted. The combination of the above sets a realistic benchmark rate of chemotherapy utilisation.

A limitation of this study is that comorbidity is not incorporated into the model. The relationship between the number and severity of comorbid conditions and any recommendations for chemotherapy is variable; it is further complicated by other issues such as age and performance status. Due to the under-representation of older patients with comorbidities in clinical trials of chemotherapy, there is no clear evidence on whether or not these patients would benefit from treatment. Gross et al. reported that adjuvant chemotherapy provided a significant survival benefit to older patients with Stage III colon cancer and heart failure, COPD or diabetes.[41] In view of the lack of evidence, comorbidity is not considered in the optimal chemotherapy utilisation tree. Secondly, our estimates of performance status were derived from the general population and we have made the assumption that the initial performance status is similar in all stages; both of these could lead to an overestimation of the optimal rate. In the absence of performance status data, we have tried to counter this by conducting sensitivity analysis with a lower proportion of good performance status patients. Thirdly, three of four of the sources used for comparison between optimal and actual utilisation rates refer to the year 2000 and therefore may not be representative of current chemotherapy utilisation rates.

In conclusion, the estimated optimal chemotherapy utilisation rate serves as an important evidence-based benchmark for the quality of cancer care for colon cancer. Whereas current benchmarks of quality in colorectal cancer care focus on whether patients in Stage III colon cancer receive chemotherapy, we have found that the biggest area of underutilisation of chemotherapy is in Stage IV colorectal cancer. The reasons for patient refusal of chemotherapy should be further investigated in future studies.

Conflict of interest statement

None declared.

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