Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect


Published in:
Gut

Citation for published version (APA):
Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect

W H de Vos tot Nederveen Cappel, E Buskens, P van Duijvendijk, A Cats, F H Menko, G Griffioen, J F Slors, F M Nagengast, J H Kleibeuker and H F A Vasen

Gut 2003;52;1752-1755
doi:10.1136/gut.52.12.1752

Updated information and services can be found at:
http://gut.bmjournals.com/cgi/content/full/52/12/1752

These include:

References
This article cites 19 articles, 3 of which can be accessed free at:
http://gut.bmjournals.com/cgi/content/full/52/12/1752#BIBL

3 online articles that cite this article can be accessed at:
http://gut.bmjournals.com/cgi/content/full/52/12/1752#otherarticles

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Topic collections
Articles on similar topics can be found in the following collections

Gastrointestinal Surgery (251 articles)
Cancer: gastroenterological (1219 articles)
Genetics (3947 articles)

Notes

To order reprints of this article go to:
http://www.bmjournals.com/cgi/reprintform

To subscribe to Gut go to:
http://www.bmjournals.com/subscriptions/
**COLON CANCER**

Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect

W H de Vos tot Nederveen Cappel, E Buskens, P van Duijvendijk, A Cats, F H Menko, G Griffioen, J F Slors, F M Nagengast, J H Kleibeuker, H F A Vasen

---

**Background:** In view of the high risk of developing a new primary colorectal carcinoma (CRC), subtotal colectomy rather than segmental resection or hemicolectomy is the preferred treatment in hereditary non-polyposis colorectal cancer (HNPCC) patients. Subtotal colectomy however implies a substantial decrease in quality of life. To date, colonoscopic surveillance has been shown to reduce CRC occurrence.

**Aims:** To compare the potential health effects in terms of life expectancy (LE) for patients undergoing subtotal colectomy or hemicolectomy for CRC.

**Methods:** A decision analysis (Markov) model was created. Information on the 10 year risk of CRC after subtotal colectomy (4%) and hemicolectomy (16%) and stages of CRCs detected within a two year surveillance interval (32% Dukes’ A, 54% Dukes’ B, and 14% Dukes’ C) were derived from two cohort studies. Five year survival rates used for the different Dukes stages (A, B, and C) were 98%, 80%, and 60%, respectively. Remaining LE values were calculated for hypothetical cohorts with an age at CRC diagnosis of 27, 47, and 67 years, respectively. Remaining LE values were also calculated for patients with CRC of Dukes’ stage A.

**Results:** The overall LE gain of subtotal colectomy compared with hemicolectomy at ages 27, 47, and 67 was 2.3, 1, and 0.3 years, respectively. Specifically for Dukes’ stage A, this would be 3.4, 1.5, and 0.4 years.

**Conclusions:** Unless surveillance results improve, subtotal colectomy still seems the preferred treatment for CRC in HNPCC in view of the difference in LE. For older patients, hemicolectomy may be an option as there is no appreciable difference in LE.

---

**H**ereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant disorder predisposing to cancer. It has been estimated that 2–5% of all cases of colorectal cancer (CRC) are due to HNPCC. Identification of the DNA mismatch repair (MMR) genes responsible for the disease has facilitated diagnosis of HNPCC and made it possible to identify carriers of the mutated gene within a family. These carriers have a high risk of developing CRC, endometrial cancer, and other cancers associated with HNPCC. One of the hallmarks of the syndrome is the occurrence of multiple tumours in an individual. These include multiple primary CRCs or the combined occurrence of CRCs, endometrial cancer, and other related cancers. The risk of developing a metachronous CRC was estimated to be 20–30% within 10 years after treatment of the first CRC. This forms the basis for the recommendation to perform colectomy with an ileorectal anastomosis (that is, subtotal colectomy) in patients with CRC due to an MMR gene defect.

Recently, a number of studies on the effectiveness of periodic examination of the colorectum have been published. Jinne et al reported that surveillance led to a 56% reduction in the CRC rate in a group of screened mutation carriers compared with a group of carriers that did not undergo surveillance examinations. A recent study on 114 Dutch families showed that regular colonoscopic surveillance leads to the identification of mainly local tumours. Subtotal colectomy performed for CRC leads to a significant reduction in quality of life (QOL) compared with the general population. The SCOTIA group prospectively compared the difference in QOL after subtotal colectomy and segmental resection in sporadic CRC. They concluded that segmental resection was associated with fewer bowel function problems and therefore was the preferred treatment in left sided malignant colonic obstruction.

In view of the above findings the question rises whether subtotal colectomy remains the preferred treatment in HNPCC patients with a primary CRC. The main goal of this study was to compare the potential health effects in terms of life expectancy (LE) between patients that underwent subtotal colectomy followed by surveillance of the rectum, and those that underwent a more conservative surgical procedure (that is, segmental resection or hemicolectomy) followed by surveillance of the remaining bowel.

**METHODS**

**Markov model**

A Markov model was constructed using DATA 3.5 (TreeAge Software, Inc., Williamstown, Massachusetts, USA) to compare different treatment strategies for CRC in HNPCC patients. In brief, a model was constructed comprising the possible health states of a patient (patient with a Dukes’ A, B, or C tumour). Subsequently, all relevant possible health transitions were recognised. The likelihood of transferring from the original health state to the next over time is reflected by transition probabilities—that is, the chance of transition from one state to another state (for example, patients may develop a second tumour after surgery for their...
first CRC). The state to state transition was characterised by a
probability distribution (based on the chance of developing a
second CRC derived from literature study). The model follows
a hypothetical cohort of mutation carriers over time and
tracks the annual incidence of CRC by stage and mortality.
Short term mortality associated with surgery was also
incorporated.

Remaining LE was calculated after three different types of
surgical approaches for CRC: (1) proctocolectomy with
ileoanal anastomosis that was assumed to eliminate all risk
of CRC and the need for postoperative surveillance; (2)
subtotal colectomy with ileorectal anastomosis followed by
surveillance of the rectum; and (3) partial colectomy—that is,
segmental resection or hemicolectomy followed by surveil-
ance of the remaining bowel. Surveillance was defined as
colonoscopy every two years after segmental resection or
hemicolectomy and flexible sigmoidoscopy of the remaining
rectal segment every two years after subtotal colectomy.
Primary model outcome was the LE. In addition, we
differentiated between survivals with various parts of the
colon intact. Remaining LE values for a mutation carrier were
calculated after the three different types of surgical proce-
dures at the age of CRC detection of 27 years, 47 years, and 67
years.

Data sources and assumptions
The probabilities and pertaining sources used in the Markov
model are listed in table 1.

Risks of a metachronous CRC after surgery
(1) Proctocolectomy was assumed to eliminate all risk of
CRC.
(2) The risk of rectal cancer after subtotal colectomy varies
across studies and ranges from 3.4% to 10% every 10 years.9–11
On the basis of the most recent study, the risk of rectal cancer
after subtotal colectomy was assumed to be 4% after 10 years.
(3) The risk of a metachronous tumour after partial
colectomy varies from 15% to 30%.2–4 On the basis of our
own recent data, we estimated the risk of CRC after
segmental resection at 16% after 10 years.

Colorectal cancer stages
Information on the stages of CRCs when detected by
surveillance was derived from two large scale studies from
the Netherlands and Finland. The distribution of the stages
detected ≤2 year after a negative surveillance examination
while on the Dutch or Finnish surveillance program were
used, as shown in table 1 (Dukes’ A 32%, Dukes’ B 54%, and
Dukes’ C 14%).

Survival and mortality
Information on colorectal carcinoma survival was derived
from recent studies on survival in HNPCC patients.13–14 Five
year survival rates were assumed to be 98% in the case of
Dukes’ A, 80% for Dukes’ B, and 60% for Dukes’ C.15 We
assumed a preoperative mortality rate of 0.5%.15–18

RESULTS
If cancer is detected while on the surveillance program,
proctocolectomy with ileoanal anastomosis will lead to the
greatest LE of 47.1 years for a mutation carrier at age 27
years. Subtotal colectomy with ileorectal anastomosis leads to
an LE of 45.8 years whereas segmental resection or
hemicolectomy leads to an LE of 41.6 years. The benefit of
subtotal colectomy compared with segmental resection or
hemicolectomy decreases as CRC is detected at an older age.
The LE gain of subtotal colectomy compared with segmental
resection or hemicolectomy is 2.3 years at age 27 years, one
year at age 47 years, and 0.3 years at age 67 years.

If the first CRC detected while on the screening program is
a Dukes’ stage A carcinoma, proctocolectomy with ileoanal
anastomosis will lead to the greatest LE of 47.1 years for a
mutation carrier at age 27 years. Subtotal colectomy with
ileoanal anastomosis leads to an LE of 45.8 years whereas
segmental resection or hemicolectomy leads to an LE of 42.4
years. The LE gain of subtotal colectomy compared with
segmental resection or hemicolectomy is 3.4 years at age 27
years, 1.5 years at age 47 years, and 0.4 year at age 67 years.

Note however that this survival is conditional on the tumour
being Dukes’ stage A. Information on exact stage is not
available prior to operation and therefore the survival benefit
cannot be considered representative. In table 2, the LE values
of all possible surgical options are shown for different Dukes’
stages.

DISCUSSION
Since the identification of the genes responsible for HNPCC,
clinicians are more aware of this condition and, consequently
an increasing number of families are recognised. An
important question is whether the clinical management of
CRC, associated with HNPCC, should differ from that of
sporadic CRC. Until now, there was general agreement that
subtotal colectomy was the preferred surgical treatment for a
patient from a well defined HNPCC family with an early CRC.
The rationale for this recommendation is the significant risk
of developing a subsequent metachronous CRC, reported by
several research groups.16–18 However, a recent study showed
that periodic colonoscopic examinations of family members
at high risk for HNPCC led to a significant reduction in the
CRC rate.7 The vast majority of tumours, detected by
surveillance, were in an early stage. Another recent study
showed that subtotal colectomy in patients with familial
adenomatous polyposis led to a significant reduction in QOL
compared with the general population.19 With respect to this
observation, it should be realised that QOL may be better
after subtotal colectomy in HNPCC patients than in patients
with familial adenomatous polyposis because in the latter

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dukes’ A</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Dukes’ B</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Dukes’ C</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer 5 year survival rates</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Dukes’ A</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Dukes’ B</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Dukes’ C</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

CRC, colorectal cancer.
ileoanal anastomosis appears to be the treatment of first choice. However, the risk of developing a second CRC is relatively low. As a consequence, in these patients we consider segmental resection as an appropriate surgical option. In general, subtotal colectomy should be avoided in a patient with a history of poor sphincter function. When choosing partial colectomy, it is very important to rule out the occurrence of a synchronous tumour. Unfortunately, studies on QOL after different surgical treatments do not specifically consider HNPCC patients. For these patients, the risk of a synchronous or metachronous tumour after a limited resection might have a considerable impact on QOL due to fear of cancer. This argument may also be used in decision making.

Table 2  Life expectancy of patients with colon cancer depending on treatment offered and age at first detection

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Age 27 y</th>
<th>Age 47 y</th>
<th>Age 67 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemicolectomy overall</td>
<td>31.6</td>
<td>20.6</td>
<td>10.5</td>
</tr>
<tr>
<td>Subtotal colectomy overall</td>
<td>33.9</td>
<td>21.6</td>
<td>10.8</td>
</tr>
<tr>
<td>Proctocolectomy overall</td>
<td>34.8</td>
<td>21.9</td>
<td>10.8</td>
</tr>
<tr>
<td>Hemicolectomy Dukes’ A</td>
<td>42.4</td>
<td>27.4</td>
<td>13.7</td>
</tr>
<tr>
<td>Subtotal colectomy Dukes’ A</td>
<td>45.8</td>
<td>28.9</td>
<td>14.1</td>
</tr>
<tr>
<td>Proctocolectomy Dukes’ A</td>
<td>47.1</td>
<td>29.4</td>
<td>14.2</td>
</tr>
<tr>
<td>Hemicolectomy Dukes’ B</td>
<td>29.1</td>
<td>19.0</td>
<td>9.8</td>
</tr>
<tr>
<td>Subtotal colectomy Dukes’ B</td>
<td>31.1</td>
<td>19.8</td>
<td>10.0</td>
</tr>
<tr>
<td>Proctocolectomy Dukes’ B</td>
<td>31.8</td>
<td>20.1</td>
<td>10.0</td>
</tr>
<tr>
<td>Hemicolectomy Dukes’ C</td>
<td>16.9</td>
<td>11.3</td>
<td>6.2</td>
</tr>
<tr>
<td>Subtotal colectomy Dukes’ C</td>
<td>17.6</td>
<td>11.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Proctocolectomy Dukes’ C</td>
<td>18.0</td>
<td>11.7</td>
<td>6.2</td>
</tr>
</tbody>
</table>

*Overall takes into account a distribution of Dukes’ stages A, B, and C of 32%, 54%, and 14%, respectively.

For detection of CRC in patients with a suspected family history of HNPCC, immunohistochemical expression analysis of MMR proteins and/or microsatellite instability analysis on biopsies taken at colonoscopic examinations are useful tools to confirm the presence of microsatellite instability. In view of the above results, it may be of interest to a patient to use these molecular genetic tools before deciding on surgical treatment.

In conclusion, although intensive surveillance of HNPCC patients reduces the incidence of CRC and overall mortality, there remains a substantial risk of developing (mainly early) CRC while on a program. If CRC is detected while on a program, in young patients (<60 years) subtotal colectomy seems to be the treatment of choice in view of the difference in life expectancy between the two options and the possible decrease in cancer fear as the risk of secondary cancer decreases. In older patients, segmental resection is also an appropriate option and should be discussed with the patient. Large prospective clinical studies should be considered to confirm our findings. Also, future studies should address how the fear of a second cancer after limited surgery influences quality of life.

ACKNOWLEDGEMENTS

The research was supported by the Netherlands Organisation for Health, Research, and Development (ZonMw).
REFERENCES


