Post-treatment surveillance in colorectal cancer

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Background. Though the post treatment surveillance of patients with colorectal cancer (CRC) treated with curative intent is common practice, its value is controversial. In the absence of conclusive clinical data, various modalities for the routine follow-up of patients with CRC have been proposed. In practice, the guidelines across countries and regions differ and are influenced by different health care policies, resource availability and doubts about effectiveness of follow-up.

Conclusions. The results of metaanalyses of available clinical trials demonstrated a survival benefit of intensified monitoring, but the questions regarding the optimal frequency of visits and the examinations to be performed remain unanswered. Furthermore, intensive monitoring of CRC survivors may be difficult to be administrated, causes discomfort and morbidity to the patient and can have serious cost-implications to the healthcare system. However, as it seems from available data, a comprehensive surveillance program does not affect the quality of patients’ life. Ongoing large prospective multi-institutional randomised trials might elucidate some of the crucial questions and existing dilemmas to establish adequate surveillance strategy for CRC patients.

Key words: surveillance; colorectal cancer

Introduction

Colorectal cancer (CRC) is a significant public health problem. In Slovenia, CRC is the second most frequently diagnosed cancer in both men and women and the second leading cause of cancer death, with estimated 1,284 new cases and 682 related deaths in 2006. Five year relative survival in 2005 was 57.7% for colon cancer and 45.4% for rectal cancer, increasing by 16.2% and 11.4%, respectively, from 1991. Over the last two decades, CRC research has lead to better understanding of disease behaviour, resulting in more efficient treatments and higher prevalence of cancer survivors. In spite of radical treatment, approximately 30-50% of patients will develop recurrent disease of whom only 5-30% would be considered eligible for further surgery; of those only 3-5% will be actually cured. In addition, the reported rates of second primary tumours in CRC patients are ranging from 5% to 10%. Furthermore, long-term analyses of Scandinavian trials have shown an increased risk of second cancers in the patients treated with preoperative radiotherapy for rectal cancer in organs within or adjacent to the irradiated volume.

The main aim of post-treatment surveillance after potentially curative treatment of CRC is to improve survival through early detection of polyps and new primaries or recurrent tumours when efficient treatment is possible. Secondary goals are to assess the efficacy of initial treatment, management of long-term post-treatment complications, to offer comprehensive psychologic support and support in disease prevention.

Studies of CRC follow-up strategies

To define the value of varying levels of follow-up intensity in surveillance programs among CRC survivors, six randomized controlled trials were conducted (Table 1). Two of them have showed a survival benefit from more intensive follow-up. There was a great variability between the
studies in defining the follow-up. For example, the kind of follow-up that was considered as “intensive” in the study by Makela et al., was assessed by Shoemaker et al. as “less intensive”. In some of the studies, the sample size was not sufficient to detect survival differences with different surveillance strategies, and some of the studies included patients with stage I disease. Therefore, some meta-analysis were performed as a systematic approach to identification and abstraction of critical information from different randomised, controlled trials. Two meta-analyses of five randomised trials identified a survival advantage for the patients followed more intensely as significantly higher incidence of asymptomatic local or systemic recurrence was recognized among the patients monitored closely and, consequentially, reoperation for cure was more frequent in this group. These results were confirmed by another, recently published meta-analysis including six randomised trials on this topic with a significant improvement in survival favouring more intense follow-up (Relative Risk Ratio 0.80; 95%CI, 0.70 to 0.91; p = 0.0008). A significant improvement in survival was observed only those trials which included CEA testing and/or liver imaging. Another two meta-analyses (on randomised and nonrandomised trials) concluded that intensive follow-up programmes can improve survival and should be “individualised” according to a person’s characteristics.

In an attempt to rationalize CRC follow-up, three prospective multi-institutional randomised trials comparing more intensive with less intensive monitoring are being carried out at the moment: the FACS trial in United Kingdom, the FFCD trial in France and the GILDA trial in Italy. The GILDA follow-up schemes are presented in Table 2. The results of these trials are pending.

Potential limitations of follow-up

Few considerations have to be taken into account when promoting surveillance and there are some limitations to this approach.

First, there is a small risk of adverse events associated with colonoscopy itself or with polipectomy during the follow-up. Only one of the prospective randomised follow-up studies reported these data: two perforations and two gastrointestinal haemorrhages from a total of 731 colonoscopies.

Secondly, frequent visits to physician might be inconvenient to the patients and even harmful due to unnecessary exposition to radiation. Fear of recurrence or unnecessary stress resulting from false positives results may also have a negative impact on the quality of their lives. False positive results are on average 16 times (0.2-200) more common than true positive results. On the other hand, reassuring effect of normal test results and psychological support from physician might be beneficial. The data about the effect of follow-up on patients’ health-related quality of life (HRQL) are limited and conflicting. While Stiggelbout et al. and Wattchow et al. indicated that HRQL was not improved through follow-up visits, Kjeldsen et al. demonstrated a small but significant increase in HRQL with a more intensive follow up.

The third factor to be taken into consideration when promoting surveillance is high cost of such program. A wide variety of follow-up schemes are associated with large differences in costs. Few studies focused on this issue. Virgo et al. reported a 28-fold difference in costs between minimal and

<table>
<thead>
<tr>
<th>Studies</th>
<th>Year</th>
<th>No</th>
<th>CEA testing</th>
<th>Liver imaging</th>
<th>5-y OS IFU</th>
<th>P value</th>
</tr>
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<tr>
<td>Makela17</td>
<td>1995</td>
<td>106</td>
<td>Yes</td>
<td>Yes</td>
<td>59 (54)</td>
<td>0.26</td>
</tr>
<tr>
<td>Ohlsson18</td>
<td>1995</td>
<td>107</td>
<td>Yes</td>
<td>No</td>
<td>75 (67)</td>
<td>0.50</td>
</tr>
<tr>
<td>Kjeldsen19</td>
<td>1997</td>
<td>597</td>
<td>No</td>
<td>No</td>
<td>68 (70)</td>
<td>0.48</td>
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<tr>
<td>Schoemaler20</td>
<td>1998</td>
<td>325</td>
<td>No</td>
<td>Yes</td>
<td>76 (70)</td>
<td>0.20</td>
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<tr>
<td>Pietra21</td>
<td>1998</td>
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<td>73 (58)</td>
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<tr>
<td>Secco22</td>
<td>2002</td>
<td>358</td>
<td>Yes</td>
<td>Yes</td>
<td>62 (43)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Abbreviations: No = number of patients; OS = overall survival; IFU = intensive follow-up.
most extensive 5-year follow-up in USA, ranging from US$ 910 to US$ 26,717. Audisio et al. calculated the 5-year follow-up costs in Italy as follows: US$ 3,800 per patient; US$ 13,580 for each recurrence; US$ 59,841 for every recurrence treated for cure and US$ 13,677 for each cured patient; the difference in costs between minimal and aggressive 5-year follow-up protocol was US$ 4,800 per patient. Authors recommended that the programmes should be tailored to the stage and site of primary cancer in order to reduce costs and that controlled economic studies are required. The cost-effectiveness analysis of five randomized trials showed that the cost for the intensive follow-up resulted in a net extra cost of US$ 4,214–4,299 per patient compared with the less intensive follow-up arm. Each life year saved through the intensive follow-up was calculated to cost between US$ 5,230–5,783.

When resectability of recurrences was considered, a cost minimization analysis performed by Rodrigues et al. demonstrated that the cost per resectable tumour recurrence was lower in the intensively followed group. This is a logical conclusion despite the fact that the overall cost of intensive follow-up was higher in the intensive strategy group than in less intensive one.

Other authors pointed to the high cost of follow-up suggesting that it should be transferred to the primary care setting. The arguments were that the specialist care is more intense and that specialists tend to propose more expensive follow-up strategies.

The question remains, who should carry out the follow-up visits. With increasing numbers of CRC survivors, primary care physicians (PCPs) are more and more engaged in CRC follow-up programs. The data from the literature regarding the utility of general versus specialist care in CRC survivors are sparse. In a study by Nissen et al., PCPs reported dissatisfaction with this transfer of care for survivors; they also felt uncertain about the appropriate frequency and duration of surveillance testing for cancer recurrence. Moreover, in a recently published study by Snyder et al., the authors reported a decreased intensity of cancer-related screening program as oncologists were becoming less involved in survivor care. The survivors followed up by both a PCP and an oncologist were most likely to receive both noncancer-related recommended care and cancer surveillance. The authors concluded that a shared model of survivorship care should be developed with a clear and detailed description of roles of both sides, PCP’s and oncologist’s, to gain maximal coordination and efficacy. On the other hand, some data suggest that the survivors followed up by PCP only did not perceive lower qua-

### TABLE 2. GILDA trial for rectal cancer follow-up

<table>
<thead>
<tr>
<th>Months from randomisation</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
<th>60</th>
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<tbody>
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<tr>
<td>Office visit</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>CEA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
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<tr>
<td>Colonoscopy</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>Chest X-ray</td>
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<tr>
<td>Liver ultrasound</td>
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<td><strong>More Intensive</strong></td>
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<tr>
<td>Office visit</td>
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<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Blood tests</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Colonoscopy</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>Chest X-ray</td>
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<tr>
<td>Liver ultrasound</td>
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<tr>
<td>Abdominal-pelvic CT</td>
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</tbody>
</table>

Abbreviations: blood tests include complete blood count, liver tests, tumour markers CEA and Ca 19-9.
lity of care\textsuperscript{10}, which was also confirmed by others mentioning that no difference was recorded in the rate of recurrence and death as well as time to detection of recurrence in comparison to the patients followed by a surgeon or PCP.\textsuperscript{45}

Finally, with respect to cost and time consumption of follow-up, it seems reasonable that the surveillance of patients for whom additional therapeutic options when recurrence occurs are available\textsuperscript{4,46}, should be more intense. Furthermore, particular attention was paid to determine the subgroups of CRC patients which might benefit the most from follow-up with regard to tumour site or stage. The results of a prospective randomized trial on 259 CRC survivors conducted by Rodrigues-Moranta et al. indicated that the patients with stage II tumours or lesions in the rectum had higher overall survival when followed more intensively than those on less intensive follow-up program. No difference was found between the patients with stage III lesions or lesions located in colon.\textsuperscript{38}

### Current recommendations and adherence to them by physicians

Several guidelines have been published on the surveillance of CRC survivors. Follow-up program is recommended by all leading professional societies, e.g. the American Society of Clinical Oncology (ASCO)\textsuperscript{47}, National Comprehensive Cancer Network (NCCN)\textsuperscript{48,49} and European Society Medical Oncology (ESMO)\textsuperscript{50,51}. Surveillance protocols include regular outpatient’s visits followed by physical examination, CEA monitoring, radiological and endoscopic examinations. It must be stressed that none of diagnostic procedures by itself is sensitive or specific enough to detect the recurrence at early, treatable stage; so, the guidelines recommend different packages of tests.

Although there are differences in frequency, intensity and combinations of investigations as proposed by various programs, some parts of recommendations are similar (Table 3). Monitoring is more intense during the first two to three years after radical treatment, as most of the recurrences

### TABLE 3. Follow-up guidelines of main professional societies

<table>
<thead>
<tr>
<th>Modality</th>
<th>ASCO\textsuperscript{47}</th>
<th>NCCN\textsuperscript{48,49}</th>
<th>ESMO\textsuperscript{50,51}</th>
</tr>
</thead>
<tbody>
<tr>
<td>History, physical exam</td>
<td>Every 3-6 m for 3 y, then every 6 m up to 5 y</td>
<td>Every 3-6 m for 2 y, then every 6 m up to 5 y</td>
<td>every 3-6 m for 3 y, then every 6-12 m for 2 y (colon) every 6 m for 2 y (rectal cancer)</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>at 3 y, every 5 y thereafter</td>
<td>At 1 y, then at 3 y, every 5 y thereafter</td>
<td>After 1 y, then every 3 y (colon) every 5 y (rectal cancer)</td>
</tr>
<tr>
<td>Flexible proctoscopy (rectal cancer)</td>
<td>every 6 m for 5 y (for not irradiated patients)</td>
<td>every 6 m for 5 y (for patients with LAR)</td>
<td>every 6 m for 2 years</td>
</tr>
<tr>
<td>Blood tests</td>
<td>not recommended</td>
<td>not recommended</td>
<td>not recommended</td>
</tr>
<tr>
<td>CEA</td>
<td>every 3-6 m for 3 y (stage II and III)</td>
<td>every 3-6 m for 2 y, then every 6 m up to 5 y (staged as T2 or greater)</td>
<td>if initially elevated: every 3-6 m for 3 y, then every 6-12 m for 2 y (colon) not recommended (rectal cancer)</td>
</tr>
<tr>
<td>Chest x-rays</td>
<td>not recommended</td>
<td>not covered</td>
<td>not recommended</td>
</tr>
<tr>
<td>US abdomen</td>
<td>not covered</td>
<td>not covered</td>
<td>not recommended</td>
</tr>
<tr>
<td>CT thorax and CT abdomen</td>
<td>annually for 3 y for pts with high risk of recurrence</td>
<td>annually for 3-5 y for stage II and III</td>
<td>Every 6 m for 3 y for pts with high risk of recurrence (colon) Not recommended (rectal cancer)</td>
</tr>
<tr>
<td>Pelvic CT (rectal cancer)</td>
<td>negative prognostic features, especially for not irradiated pts (no frequency)</td>
<td>Not covered</td>
<td>not recommended</td>
</tr>
</tbody>
</table>

Abbreviations: m=months; y=years; ASCO=American Society Clinical Oncology; NCCN=National Comprehensive Cancer Network; ESMO=European Society Medical Oncology
Conclusions

Follow-up of CRC survivors is a common practice. Intensive surveillance enhances the probability of diagnosing precancerous lesions, recurrences or new primaries at early stage when the existing treatment options could be used with curative intent. Consequently, comprehensive surveillance program improves the survival and at the same time – as it seems from available data, does not affect the quality of patients’ life. On the other hand, the increased costs and time consumption of intensive surveillance limit its utility. Due to limited, and to some extent conflicting data, there are no uniform guidelines for the CRC survivors regarding the frequency of visits and tests to be performed at each visit. Ongoing large prospective multi-institutional randomised trials might elucidate some of the crucial questions and existing dilemmas to establish an adequate surveillance strategy for CRC patients.

Acknowledgement

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References


