Cancer, thrombosis and low-molecular-weight heparins
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CHAPTER 7

*Screening for occult cancer in patients with idiopathic venous thromboembolism: Yes.*

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Debate

The strict two-way clinical relationship between cancer and venous thromboembolism (VTE) is well recognized since Trousseau's time and has been over time confirmed and documented (1). There is, accordingly, firm evidence of the increased risk of subsequent clinically overt malignancy during the follow-up of patients experiencing a venous thrombotic event, when compared to general population, particularly in patients with idiopathic VTE (2–9) (Table 1). Newly discovered malignancies involve virtually all body systems (10). Moreover, two recently published large population-based registries (11,12) have provided clear evidence that the incidence of cancer is increased in patients with VTE during the first year of follow-up. They, in fact, provided a SIR of newly diagnosed cancers in the first year, as compared to general population, as high as 4.4 and 2.1, respectively. Despite the conclusive evidence of the strong relationship between idiopathic VTE and the risk for hidden cancer, the need to screen for occult malignancy in this category of patients is still unclear. In fact, before recommending an extensive screening in this setting we need to know which is the percentage of cancers that can be detected and at which stage they are detected. In addition, as the extensive screening might suffer from discomfort and morbidity from procedures themselves, together with high costs, it may be widely recommended only if it demonstrates a favourable impact on cancer natural history.

The SOMIT Study

With the aim of giving a contribution to this important problem and to provide information on the most important tests to be performed in this respect, we have undertaken a multicenter randomized clinical trial comparing the strategy of an extensive screening (Table 2) vs. no further testing for malignant disease (13). Hence, 201 patients with idiopathic VTE in whom a routine initial evaluation did not reveal malignancy were randomly allocated to either extensive diagnostic screening (n = 99) or no further testing (n = 102), and were followed up for 2 years. In the extensive screening group, 13 patients (13.1%) had an early detection of a histologically confirmed malignancy (in 10 cases revealed by CT scan of the abdomen and pelvis), and a further malignancy (1.0%) became apparent during follow-up. Therefore, 13 of the 14 malignancies that became apparent in the extensive screening group were identified at the time of screening, for a sensitivity of initial screening of 93%. In the control group, a total of 10 (9.8%) malignancies became symptomatic during follow-up. Most of the malignancies were detected at an earlier stage in patients belonging to the extensive screening group. The risk of occult cancer was higher in elderly patients and in those without thrombophilic conditions. Cancer-related mortality occurred in two (2.0%) of the 99 patients of the extensive screening group vs. four (3.9%) of the 102 control patients, for an absolute difference of 1.9% (95% CI, −5.5 to 10.9%). The cluster of cancer-related mortality, presence of objectively documented residual or recurrent malignancy occurred in five (5.1%) of the 99 patients of the extensive screening group as compared to eight (7.9%) of the 102 control patients, for an absolute difference of 2.8% (95% CI, −6.3 to 13.4%). The risk of occult cancer was higher in elderly patients and in those without thrombophilic conditions. From the results of this prospective study we can say that the use of extensive screening for malignancy in patients with idiopathic VTE is worthwhile to identify hidden malignancies, since a substantial proportion of occult cancer were discovered, and many of these were in a relative early phase allowing possible curative treatment. Although the data do not demonstrate conclusively that early diagnosis as a result of screening ultimately prolongs life, the collective observations make such a beneficial effect likely.
Comment

Although a primary physician’s task should be to clarify, whenever possible, the pathophysiology of diseases occurring in patients, some authors in this setting claim that the real benefit of early cancer identification through extensive screening may vanish by the reported pending poor prognosis of these patients. In fact, the important topic, which may tip the balance from favouring to rejecting the performance of extensive screening, is the impact of any proposed screening battery on cancer natural history. In a recent study by Sorensen, the survival rate of patients whose cancer was diagnosed in the first year after the thrombotic event was compared with that of cancer patients without thrombosis (14). An increased mortality was found in the former group. Moreover, also patients in whom cancer was found at the time of hospital admission for index thrombotic event experienced a poorer prognosis.

However, given the retrospective nature of this study, it is likely that cancers were already symptomatic at the time thrombosis occurred, hence easily detectable by routine tests from patients in whom no advice of malignancy was present at the time of index VTE. This is, in our opinion, the crucial point to be considered: only thrombotic events in this latter subgroup can be labelled as idiopathic. The early detection of occult cancer at the time the disease is still totally asymptomatic might yield a more favourable clinical outcome. This assertion is in keeping with data from the SOMIT study and from available literature, which suggest that in otherwise healthy patients with an episode of idiopathic VTE, the early detection of cancer may provide more treatment possibilities to physicians. The SOMIT study has indeed found a positive, albeit not significant, impact on cancer related-mortality. It could be argued that these results may produce only a near to conjectural hypothesis, given the fact that the number of patients enrolled was insufficient to draw firm conclusions. However, the early disclosure of cancer, which might mean identification of the disease at an attackable state according to oncologic and surgical knowledge is likely to be tremendously crucial, especially nowadays when continuous echoes of innovations and discoveries on therapeutic protocols provide growing chances in terms of success and eradication of malignant diseases. In case of lacking or delayed diagnosis of cancer, the prognosis can only be worse. Since the extensive screening battery is costly to the society and may carry discomfort to patients for waiting lists, minor test-related side-effects, and psychological burden, a further step will be to limit the execution of screening procedures to patients at higher risk of harbouring an occult disease, and to implement limited screening batteries incorporating those tests which have gained the best yields in available studies.
Table 1: Incidence of occult cancer after VTR diagnosis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Cancer (All VTR)</th>
<th>Cancer (Secondary VTR)</th>
<th>Cancer (Idiopathic VTR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeka et al. [2]</td>
<td>11/83 (13.3%)</td>
<td>2/48 (4.2%)</td>
<td>9/35 (25.7%)</td>
</tr>
<tr>
<td>Prasad et al. [3]</td>
<td>13/250 (5.2%)</td>
<td>2/4/5 (1.9%)</td>
<td>11/145 (7.6%)</td>
</tr>
<tr>
<td>Ahmed et al. [4]</td>
<td>3/186 (1.5%)</td>
<td>0/83 (0%)</td>
<td>3/113 (2.7%)</td>
</tr>
<tr>
<td>Moeed et al. [5]</td>
<td>6/659 (1.2%)</td>
<td>4/63 (0.7%)</td>
<td>4/56 (4.2%)</td>
</tr>
<tr>
<td>Heitanacheli et al. [6]</td>
<td>13/326 (4.0%)</td>
<td>4/71 (1.8%)</td>
<td>10/155 (6.5%)</td>
</tr>
<tr>
<td>Ravan et al. [7]</td>
<td>21/264 (8.0%)</td>
<td>2/12 (1%)</td>
<td>13/152 (8.6%)</td>
</tr>
<tr>
<td>Schulman et al. [8]</td>
<td>111/854 (13.0%)</td>
<td>18/320 (5.6%)</td>
<td>93/534 (17.4%)</td>
</tr>
</tbody>
</table>

Table 2: Extensive screening battery in the SOMIT Study

- Ultrasound of abdomen and pelvis
- CT-scan of abdomen and pelvis
- Gastroscopy or double contrast barium swallowing
- Colonoscopy or sigmoidoscopy followed by barium enema
- Hemoccult
- Sputum cytology and tumor markers (CEA, α-FP, Ca125)
- Mammography and Pap-smear for women
- Transabdominal ultrasound of the prostate and PSA for men
References


