Hyperthermic intracavitary chemotherapy in abdomen and chest
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Prognostic value of baseline and serial Carcinoembryonic Antigen and Carbohydrate Antigen 19.9 measurements in patients with pseudomyxoma peritonei treated with cytoreduction and hyperthermic intraperitoneal chemotherapy

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Introduction

Tumor markers are useful if they facilitate diagnosis and if they can help to evaluate therapy. Pseudomyxoma peritonei is a rare disease characterized by the spread throughout the abdomen of mucus-producing cells of benign or low malignant histology, which are in most cases derived from low-grade tumors in the appendix vermiformis. These mucinous cells from enteric origin are expected to produce the proteins carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19.9), and several reports have been published showing elevated levels in patients with pseudomyxoma peritonei do occur. In The Netherlands Cancer Institute/ Antoni van Leeuwenhoek hospital, patients with pseudomyxoma peritonei are treated with aggressive cytoreduction combined with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC). In this treatment protocol, measurement of the tumor markers CEA and CA19.9 is routinely performed before treatment and at 3-month intervals afterward. In this article, we present data on the prognostic value of baseline and serial CEA and CA19.9 measurements in 63 patients with pseudomyxoma peritonei treated with aggressive cytoreduction combined with HIPEC.

Patients and methods

Between 1996 and 2001, 63 patients with pseudomyxoma peritonei were treated in The Netherlands Cancer Institute/ Antoni van Leeuwenhoek hospital. Treatment was performed according to a clearly defined treatment protocol. The diagnosis pseudomyxoma peritonei was defined by three properties. First, characteristic tumor spread was seen, with emphasis on ileocecal region, ovaries, omentum, and subdiaphragmatic regions. Second, Hounsfield measurements of tumor on computed tomography (CT) scan were compatible with high mucous content. Third, the histology showed excessive mucous with few well-differentiated cells. At laparotomy, the tumor extent was scored by region of involvement (left and right subdiaphragmatic, subhepatic, omentum/ transverse colon, small intestines/ mesentry, ileocecal, and pelvic region) and by size. Aggressive surgical cytoreduction was performed with the aim to reduce tumor residue to less than 2.5 mm. The tumor extent was again scored after the cytoreduction. Cytoreduction was considered as complete when tumor residue was less than 2.5 mm. When ≥ 2.5-mm tumor residue was left behind, the cytoreduction was considered as incomplete.

The abdomen was then lavaged with heated isotonic dialysis fluid (Dianeal™ PD1; Baxter, Uden, the Netherlands) with mitomycin C for 90 minutes (dosage of mitomycin C 35, mg/m²; temperature, 40°C-41°C). The surgical specimen was histologically examined. On the basis of the cell atypia and on the number of cells in relation to the mucous, the disease was characterized as either a benign or a malignant pseudomyxoma peritonei. Patients with malignant pseudomyxoma received, after recovery, systemic treatment with 5-fluorouracil and leucovorin for 6 months. Both CEA and CA 19.9 were routinely measured before treatment and at 3-monthly intervals after treatment.
The Liaison™ (Byk-Sangtec Diagnostica, Dietzenbach, Germany), an automated system to perform chemiluminescence immunoarrays, was used for the measurements of both CEA and CA19.9. The upper limits for normal CEA and CA19.9 are, respectively, 4 µg/L and 37 kU/L, according to the manufacturer.  

Three months after treatment, a CT scan of the abdomen was made. Frequently these CT scans showed some residual abnormalities, which were difficult to distinguish between residual tumor and postoperative changes. Recurrence was defined as increase of CT abnormalities of at least 50% in two directions, according to the World Health Organization criteria, or by cytology or histology.

In the calculation of overall survival, patients who died from any cause were counted as treatment failures; all other patients were censored at the date of their last follow-up. In the calculation of disease-free interval, patients whose disease recurred were counted as treatment failures; all other patients were censored at the date of their last follow-up. Time was measured from the date of HIPEC.

Statistical analysis was performed with SAS (Version 8 for Windows; SAS™ Institute, Cary, NC). One-way analysis of variance was used to investigate relations between baseline CEA and CA19.9 values on the one hand and the number of affected regions and type of tumor on the other hand. For number of affected regions the \(P\) value was calculated without prior amalgamation of categories (one to seven regions). Because both tumor marker values were extremely skewed to the right, a logarithmic transformation was applied before analysis. A constant of 1 was added to all values before this transformation to prevent a logarithm of 0. This transformation resulted in reasonably normally distributed residuals. A consequence of this transformation is that relative rather than absolute differences or changes were analyzed.

Survival and disease-free percentages were calculated by using the Kaplan-Meier product-limit method. Curves were compared by using the log-rank test. A stepwise procedure using the proportional hazard (PH) regression analysis was used to identify which baseline characteristics had predicting power regarding overall survival and recurrence. The inclusion and exclusion limit for the \(P\) value was .05. A logarithmic transformation of baseline CEA and CA19.9 was performed to reduce the effect of the skewed distribution on the results from the PH analysis. All variables were assumed to be linearly related with log(hazard).

A repeated-measures analysis of variance was used to analyze changes over time in the tumor markers as well as the difference between patients with and without recurrence. The relation between serial marker values and recurrence was analyzed by using PH regression with time-changing covariates. This method compares tumor marker levels at the time of recurrence with values of patients who have not yet had recurring disease at the same follow-up and translates that into a hazard ratio. The Simon-Makuch method graphically compares the survival or recurrence rate of those who remain in a particular state (e.g., normal CA19.9) with those who change from that state to another (e.g., increased CA19.9) during follow-up, but before recurrence.  

For confidence intervals (CI), the level of 68% was chosen because for the normal distribution, this coincided with \(\pm\)SE.
Results

Preoperatively increased CEA and CA19.9 levels were found in, respectively 75% (47 of 63) and 58% (35 of 60) of the patients. Baseline CA19.9 was not measured in three patients. A cross-table shows that in half of the patients, both markers are increased and that when CA19.9 is normal, CEA is increased in almost half of the cases (Table 1).

Baseline marker values and clinical characteristics

Analysis of variance indicated that both baseline CEA ($P = .0030$) and CA19.9 ($P = .0014$) are associated with the number of affected regions. The median baseline CEA in patients with one to six affected regions ($n = 23$) was 5.1 µg/L (68% CI, 3.3-7.8 µg/L), and the median baseline CA19.9 was 10.9 kU/L (68% CI, 6.8-17.4 kU/L). In patients with all seven affected ($n = 40$) regions, the baseline CEA was 43.7 µg/L (68% CI, 33.1-57.6 µg/L), and the baseline CA19.9 was 197 kU/L (68% CI, 140-278 kU/L). No differences were found between patients with benign or malignant pseudomyxoma peritonei regarding baseline CEA ($P = .35$) or CA19.9 ($P = .22$) (Table 2).

Tumor markers immediately after HIPEC

Within 3 months after cytoreduction combined with HIPEC, the tumor marker CEA normalized in 73% (22 of 30) of the patients with preoperatively increased levels, whereas for CA19.9 this percentage was 57% (16 of 28). The numbers (30 and 28) differ from the 45 and 35 mentioned for the preoperative values of CEA and CA19.9; postoperative deaths or short follow-up cause missing postoperative values.

Overall survival and baseline characteristics

Twelve patients died during follow-up after a median period of 21 months (range, 1-47 months). The median follow-up of the 51 patients still alive was 16 months (range, 0-53 months). Estimated survival at 2 years was 84% (SE, 7%) and at 3 years 67% (SE, 12%). Estimated survival at 2 year was 94% (SE, 5%) for patients with benign disease versus 62% (SE, 17%) for patients with malignant disease ($P = .013$). Patients with malignant disease

Table 1. Cross-table of preoperative CEA and CA19.9 in patients with pseudomyxoma peritonei.

<table>
<thead>
<tr>
<th></th>
<th>Normal CA19.9</th>
<th>Increased CA19.9</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CEA</td>
<td>14</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Increased CEA</td>
<td>11</td>
<td>34</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>35</td>
<td>60</td>
</tr>
</tbody>
</table>

CEA, carcinoembryonic antigen; CA, carbohydrate antigen. The upper limits for normal CEA and CA19.9 are 4 µg/L and 37 kU/L, respectively. From 3 patients of the total series ($n = 63$), either CEA or CA19.9 was known before surgery.
Table 2. Baseline marker values and number of affected regions or pathological type.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CEA (n)</th>
<th>CEA (μg/L), median (68% CI)</th>
<th>CA19.9 (n)</th>
<th>CA 19.9 (kU/L), median (68% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected regions</td>
<td>1-6 23</td>
<td>5.1 (3.3-7.8)</td>
<td>22</td>
<td>10.9 (6.8-17.4)</td>
</tr>
<tr>
<td></td>
<td>7 40</td>
<td>43.7 (33.1-57.6)</td>
<td>38</td>
<td>197 (140-278)</td>
</tr>
<tr>
<td>Pathological type</td>
<td>Benign 42</td>
<td>17.4 (12.6-23.8)</td>
<td>40</td>
<td>91.8 (62.4-134.6)</td>
</tr>
<tr>
<td></td>
<td>Malignant 21</td>
<td>29.0 (18.5-45.1)</td>
<td>20</td>
<td>39.9 (22.8-69.1)</td>
</tr>
</tbody>
</table>

CEA, carcinoembryonic antigen; CA, carbohydrate antigen; CI, confidence interval. The upper limits of normal for CEA and CA19.9 are 4 μg/L and 37 kU/L, respectively. At laparotomy, the tumor extent was scored by region of involvement (left and right subdiaphragmatic, subhepatic, omentum/transverse colon, small intestines/mesentery, ileocecal, and pelvic region). The pathological type was characterized as benign or malignant on the basis of atypia and number of cells in relation to mucous.

have a 4.4 times higher risk (95% CI, 1.4-14.2) of death with the Cox analysis compared with those with benign disease, unadjusted for other variables. When we adjust the P values at step 0 for the fact that six P values were calculated (Table 3), the P value for pathological type - increases to a nonsignificant .078. This indicates that the evidence for the existence of an association between pathological type and survival is still weak in these data. Neither marker, nor interval between diagnosis and HIPEC procedure, nor extent of disease (one to six vs. seven regions), nor cytoreduction (complete vs. incomplete) was found to be an independent prognostic factor regarding survival.

Disease-free interval and baseline characteristics

Seventeen patients were diagnosed with recurrent disease during follow-up at a median of 14 months (range, 6-46 months). The estimated disease-free probability at 2 years was 63% (SE, 10%) and at 3 years 54% (SE, 15%). The results of the stepwise procedure of the PH regression analysis are listed in Table 3 (columns 4-6).

Baseline CA19.9 and malignancy were identified as potentially independent prognostic factors with regard to recurrence. In a model with both CEA and CA19.9, the P value for CA19.9 was .026, indicating that the prognostic power CA19.9 was independent of CEA, while no independent prognostic power of CEA was found (Table 3). Figure 1 shows the disease-free interval curves for three groups of patients based on baseline CA19.9. The estimated disease-free percentage at 2 years was 94% (SE, 10%) for patients with normal CA19.9 (n = 25), versus 55% (SE, 17%) for patients with CA19.9 between 37 and 300 kU/L (n = 20) and 37% (SE, 17%) for patients with CA19.9 of ≥300 kU/L (n = 15). The hazard of recurrence is estimated to increase by 35% (95% CI, 7%–71%) per unit difference of ln(CA19.9 + 1), or approximately per 2.7-fold difference in CA19.9; e.g., from a CA19.9 of 40 kU/L to a CA19.9 of 110 kU/L. Figure 2 shows the disease-free interval curves for patients
with benign and malignant types of pseudomyxoma peritonei, adjusted for CA19.9. The estimated disease-free percentage at 2 year was 74% (SE, 9%) for patients with a benign type versus 52% (SE, 15%) for patients with a malignant type. Patients with the malignant type have a 3.0 times higher risk (95% CI, 1.05%-8.7%) of developing recurrent disease compared to patients with a benign type, with the same baseline CA19.9 value. However, when we adjust the P values at step 2 for the fact that six P values are calculated (Table 3), we do not find a P value of <.05, indicating weak evidence for the existence of an association between baseline CA19.9 and disease-free interval in our data. There is no evidence for an association between pathological type and disease-free interval. The other tested variables—interval between diagnosis and HIPEC, extent of disease, and cytore-

Table 3. P-values from stepwise proportional hazard analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival</th>
<th>Disease-free Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Step 0</td>
<td>Step 1</td>
</tr>
<tr>
<td>Interval, diagnosis to HIPEC</td>
<td>0.56</td>
<td>0.90</td>
</tr>
<tr>
<td>Extent of disease</td>
<td>0.60/0.045</td>
<td>0.41/0.25</td>
</tr>
<tr>
<td>Cytoreduction</td>
<td>0.18</td>
<td>0.35</td>
</tr>
<tr>
<td>Benign/malignant</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>Ln (CEA + 1)</td>
<td>0.18</td>
<td>0.081</td>
</tr>
<tr>
<td>Ln (CA19.9 + 1)</td>
<td>0.19</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Figure 1. Disease-free percentage by baseline carbohydrate antigen 19.9 (CA19.9). The numbers below are patients at risk. The upper limit for normal CA19.9 is 37 kU/L. The division in the groups (37-299 vs, ≥300 kU/L) was performed to obtain comparable group size. The differences between the groups are not statistically significant. HIPEC, hyperthermic intraperitoneal chemotherapy.
duction—were not found to be independent prognostic factors regarding disease-free interval.

The extent of disease was scored by region of involvement (one to seven) and was tested linearly and non-linearly. Complete cytoreduction was tested versus incomplete cytoreduction. The pathological type was characterized as benign or malignant on the basis on atypia and number of cells in relation to mucous. The intervals between diagnosis and HIPEC and both markers are linear variables. Underlined: covariates adjusted for.

**Changes in serial marker values**

Changes in serial marker values show that the CEA decreases markedly immediately after HIPEC but slowly increases again ($P < .0001$). Patients with recurrence have higher CEA values in comparison with patients without a recurrence at or before the time of measurement ($P = .0007$). However, there is only a weak evidence of a different pattern in CEA changes between patients with and without recurrence ($P = .069$). CA19.9 also decreases markedly after HIPEC ($P < .0001$). Patients with recurrence have, on average, higher CA19.9 values ($P = .0008$). There is also significant evidence that a different pattern in CA19.9 changes is related with recurrent disease ($P = .0012$).

**Serial marker values and recurrence**

The relation between serial marker values and recurrence was evaluated only for CA19.9 and not for CEA because a high $P$ value for CEA, but not for CA19.9, in the PH model was found when both markers were included. Table 4 shows that the differences between patients with regard to their CA19.9 level at a certain follow-up are reflected in an increased hazard of recurrence for the patient with the higher level. This effect is the highest for immediate recurrences: an increase in hazard by a factor of approximately 3 per 2.7-fold difference in CA19.9 +1, e.g., between a CA19.9 of 40 kU/L and a CA19.9 of 110 kU/L.

<table>
<thead>
<tr>
<th>Time of CA19.9 measurement (end point)</th>
<th>Hazard ratio (HR) per unit (increase in) ln(CA19.9 +1)</th>
<th>95% Confidence interval of HR</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At recurrence</td>
<td>3.16</td>
<td>1.99-5.03</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>3 mo before</td>
<td>1.94</td>
<td>1.32-2.85</td>
<td>.0008</td>
</tr>
<tr>
<td>6 mo before</td>
<td>1.61</td>
<td>1.15-2.26</td>
<td>.0062</td>
</tr>
<tr>
<td>9 mo before</td>
<td>1.69</td>
<td>1.15-2.49</td>
<td>.0074</td>
</tr>
<tr>
<td>12 mo before</td>
<td>1.51</td>
<td>0.98-2.31</td>
<td>.060</td>
</tr>
<tr>
<td>15 mo before</td>
<td>1.48</td>
<td>0.96-2.30</td>
<td>.079</td>
</tr>
</tbody>
</table>

CA, carbohydrate antigen. The differences between patients with regard to their CA19.9 level at a certain follow-up are reflected in an increased hazard of recurrence for the patient with the higher level. This effect is the highest for immediate recurrences: an increase in hazard by a factor of approximately 3 per 2.7-fold difference in CA19.9 +1, e.g., between a CA19.9 of 40 kU/L and a CA19.9 of 110 kU/L.
Figure 2. Disease-free percentage after first postoperatively increased carbohydrate antigen 19.9 (CA19.9). The numbers below are patients at risk. Patients with no recurrence at last follow-up were censored.

recurrences: an increase in hazard by a factor of approximately 3 per 2.7-fold difference in CA19.9 +1, e.g., between a CA19.9 of 40 kU/L and a CA19.9 of 110 kU/L. But even 9 months after differences in CA19.9 are seen, the increase in hazard of recurrence is approximately 70% for the same difference in CA19.9. The magnitude of change in the last 3 to 6 months also adds information regarding recurrence possibility, especially in the near future. During follow-up, both a high absolute CA19.9 level ($P = .0005$) and a further increase ($P < .0001$) are predictive of imminent recurrence.

Twenty-six patients had at least one elevated CA19.9 value after HIPEC. Figure 3 shows that at the moment of the first increased CA19.9 value, 4 (15%; SE, 7%) of these 26 patients already had a recurrence, increasing to 51% (SE, 13%) after 1 year and 69% (SE, 18%) after 2 years.

Simon-Makuch curves (Fig. 4A) show that patients who never attain normal CA19.9 levels have a higher recurrence rate than patients who do attain normal CA19.9 levels. Also, patients who continue to have normal CA19.9 levels rarely experience recurrence of disease (Fig. 4B) as compared with patients who have or get an increased level. In these figures, the full lines represent patients who have and continue to have abnormal CA19.9 levels (Fig. 4A) or patients who have and continue to have normal CA19.9 levels (Fig. 4B). The dotted line represents patients who have or attain normal CA19.9 levels (Fig. 4A) or patients who have or attain abnormal CA19.9 levels (Fig. 4B). During follow-up, a patient may change from the full line to the dotted line, but not the other way around.
Chapter 10

Figure 4. Simon-Makuch curves\(^a\) for disease-free percentage by carbohydrate antigen 19.9 (CA19.9). (A) Comparison of patients who continued to have increased CA19.9 values during follow-up with patients who already had or attained normal CA19.9 values during follow-up. (B) Comparison of patients who continued to have normal CA19.9 values during follow-up with patients who had or attained increased CA19.9 values during follow-up. HIPEC, hyperthermic intraperitoneal chemotherapy.

Discussion

The tumor markers CEA and CA19.9 have been used for several decades. CEA, first described by Gold and Freedman in 1965, is widely used as a tumor marker for colorectal cancer.\(^1\) The CA19.9 is a tumor-associated antigen first described by Koprowski in 1979.\(^2\) The antigenic determinant on CA19.9 that is recognized by the monoclonal antibody 116NS-19.9 is a sialylated derivative of the Lewis A antigen.\(^3\) The use of CA19.9 is well established in pancreatic and biliary disease.\(^4\) Unfortunately, it lacks sensitivity and specificity to support a diagnosis. Increased levels of CA19.9 are also seen in benign biliary and pancreatic diseases, such as inflammations, or at dysfunction of metabolism.\(^5\)

In colorectal cancer, CA19.9 shows less sensitivity but a higher specificity in comparison with CEA. Especially in advanced cancer, CA19.9 elevation is an independent prognostic factor and is a useful marker for evaluating therapy.\(^6\) Nakayama et al.\(^7\) recommend more aggressive treatment for CA19.9-positive patients. The use of different upper limits is problematic.\(^8\)
Pseudomyxoma peritonei is a separate entity characterized by the spread of mucous-producing benign or low-grade malignant cells, usually derived from a tumor in the appendix vermiformis. The spread over the abdomen has a characteristic pattern, with a clear preference for growth in the ovaries, the greater omentum, and the subdiaphragmatic regions, whereas the small bowel remains relatively unaffected. The cells are of enteric origin and the—often voluminous—tumors in the ovaries are secondary deposits.

In pseudomyxoma peritonei, tumor markers have not been studied well. Serum CEA measuring was reported to be useful during follow-up. Elevated serum CA19.9 in pseudomyxoma peritonei patients has been reported in some cases.

In our series, both preoperative CEA and CA19.9 levels were increased in a surprisingly high percentage of patients (75% and 58%, respectively). CA19.9 is known to drain via the thoracic duct toward the circulation. It is conceivable that the CA19.9 antigen produced in the peritoneal cavity, which drains directly on the thoracic duct pathway, can therefore easily reach the bloodstream. An interesting finding is that moderately and especially markedly increased preoperative CA19.9 levels seem to represent an independent prognostic factor for disease-free interval. However, we did not find any relation between baseline CA19.9 levels and histological grading of the tumor. The effect seems more likely to be an expression of the amount of CA19.9-producing cells. We found a relation between an increase of CA19.9 and disease extending over all seven regions of the abdomen. This seems to mean that more CA19.9 means more tumor load, and not surprisingly, this means worse prognosis. However, the evidence for the prognostic power of baseline CA19.9 is still rather weak because of the relatively low power of this study. Therefore, an independent confirmation seems necessary.

The massive amount of tumor present in most cases of pseudomyxoma peritonei means that marker-negative patients are probably truly negative. Partly this may be due to the little-known fact that the test of CA19.9 depends on the presence of the Lewis A antigen and that 5% to 8% of the population is unable to express the antigen. Of course, some tumors may just not express the CA19.9 antigen; however, we did not perform histological staining for CA-19.9. In the literature, no studies are reported on immunohistohemical expression of CA19.9 in patients with pseudomyxoma peritonei. It remains unclear why, in a substantial portion, CA19.9 is not expressed and why these patients seem to do better. In our series we found only one patient who had normal preoperative CA19.9 values but showed increased levels when his disease recurred. Therefore, in patients who present with massive disease and normal preoperative CA19.9 levels, it seems hardly worthwhile to continue postoperative CA19.9 monitoring. The measurement of CA19.9 is not universally applicable, and, therefore, better tumor markers with a high sensitivity and specificity are still needed.

Increasing CA19.9 levels predict an imminent clinical recurrence. In 14 patients with preoperatively increased CA19.9 levels and with increasing CA19.9 values on three successive occasions, a recurrence was eventually established. The other three patients with recurrent disease had no (known) preoperatively increased CA19.9 values (n = 2) or no CA19.9 follow-up values (n = 1). Postoperatively increased CA19.9 predated the confirmation of recurrence by CT scan or histology by a median of 9 months (median lead time). Despite the relatively
low power of this study, the evidence for a prognostic capacity of CA19.9 measurements during follow-up seems conclusive.

The predictive power of serial CA19.9 measurements with regard to survival was not tested because the relatively short follow-up period, which was at longest 5 years. The actuarial 3-year survival of patients treated with cytoreductive surgery combined with HIPEC is 81%, indicating the relatively favorable prognosis. In the future, when the duration of follow-up has increased, the predictive power of serial CA19.9 measurements with regard to survival must be analyzed.

It is interesting that despite the fact that CEA was initially increased in a higher percentage of patients, we did not find the same independent prognostic value as found for CA19.9. There was no relation between preoperative CEA and extent of tumor or prognosis. There was also a far weaker relation between recurrence and increase of CEA. This was due to a number of patients who showed both elevated CEA and CA19.9 before treatment but who at recurrence had only increased CA19.9 and normal CEA levels. When CEA and CA19.9 are both measured, CA19.9 is by far the most useful marker in pseudomyxoma peritonei.

On the basis of our observations, we recommend pretreatment measurement of CA19.9 in patients with pseudomyxoma peritonei and in case of patients with pretreatment increased CA19.9, the use of CA19.9 as marker is valuable during follow-up after therapy. If CA19.9 raises, these patients are suspect for recurrent disease.

References

Prognostic value of baseline and serial CEA and CA19.9


