Background: Colorectal cancer is one of the most common forms of cancer in the Western world. A wide variety of prognostic factors for colorectal cancer have been identified. There is, however, a paucity of literature addressing the influence of multiple primary carcinomas on prognosis. We conducted the present study in order to investigate the influence of second or multiple primary tumours on the prognosis of colorectal cancer patients.

Patients and Methods: From 1992 to 2005, 1500 patients underwent surgery for colorectal cancer at the University Hospital of Luebeck. Of these, 276 patients (19%) had multiple primary malignant tumours. We performed statistical analyses only on patients who underwent surgery with curative intent in order to minimise additional prognostic factors. The patients were divided into groups according to the time of multiple primary tumour occurrence. Data were analysed for various variables. Results: We did not detect any significant differences in survival either between the various groups or between patients with and without multiple primary tumours. Conclusion: The presence of multiple primary carcinomas is not an independent prognostic factor in patients with an index tumour of the colorectum. Multiple primary tumours are thus not necessarily associated with a poorer outcome and patients should receive curative intent surgery and appropriate follow-up care.

Key words: colorectal cancer, multiple primary carcinomas, prognostic factor

INTRODUCTION

Colorectal cancer is the second most common form of cancer and the second most common cause of cancer death in the Western world. A variety of prognostic factors for colorectal cancer have already been investigated and reported in the literature. Important factors are, for example, the degree of tumour spread according to the TNM classification system, histological differentiation, and the type of surgical intervention (R0 resection). There is, however, a paucity of literature addressing the influence of multiple (local or extracolonic) primary carcinomas on the prognosis of patients with primary colorectal cancer.

The case of a patient with multiple carcinomas was first reported by Kraske in 1884. Until the comprehensive study of 1259 case reports by Warren and Gates in 1932, multiple primary carcinomas were considered to be rare. The literature distinguishes between multiple primary carcinomas and second or double primary carcinomas. Multiple primary carcinomas are defined as second primary malignant tumours that are histologically different from the initial cancer, occur at a different location, and represent neither metastatic nor recurrent tumours from the first malignancy. Unlike multiple primary carcinomas, second or double primary carcinomas can affect the same organ but are anatomically separated from the initial tumour and thus represent neither a metastatic nor a recurrent tumour from the first malignancy.

The incidence and relative risk of developing multiple primary cancers are known to have increased. Possible explanations are an increase in life expectancy, advancements in diagnostic techniques, and an increasing number of patients undergoing surgery with curative intent. In the literature, the reported prevalence of second primary tumours in patients with primary carcinomas of the colorectum varies between 4.3% and 10%.

Against this background, we conducted a study to investigate whether the presence of second or multiple primary carcinomas influences the prognosis of colorectal cancer patients and to assess the role of the time of occurrence of
the second primary tumour (synchronous or metachronous tumours).

**PATIENTS AND METHODS**

From 1992 to 2005, 1500 patients underwent surgery for colorectal cancer (index tumour) at our institution. Colorectal resection was performed with curative intent in 1118 patients (74.5%) and with palliative intent in 382 patients (25.5%). Curative resection was defined as the complete removal of all tumours with microscopically negative resection margins (R0 resection).

The index tumour was found in the colon in 825 patients (55%), in the rectum in 650 patients (43.3%), and in both the colon and rectum in 24 (1.6%). The location of the index tumour was unknown in 1 patient.

The index tumour was managed by resection with preservation of faecal continence in 85% of the patients (n=1277), extirpation in 6.5% (n=98), pelvic exenteration in 0.5% (n=7), and local resection in 2.4% of the cases (n=36). Cryosurgery or laser surgery was performed in 1.4% (n=21). A stoma was created in 2.8% (n=42) and palliative bypass surgery was performed in 1.3% of the patients (n=19).

The patients were divided into groups according to the time of occurrence of their multiple primary carcinomas. Second primary tumours were defined as premetachronous when they occurred 6 months or more before the index tumour. Second primaries that were diagnosed within 6 months before and 3 months after the occurrence of the index tumour were described as synchronous. Second primary tumours were defined as postmetachronous when they occurred 3 months or more after the index carcinoma.

Patients who met the Bethesda guidelines or the Amsterdam criteria for hereditary nonpolyposis colorectal cancer (HNPCC) as well as patients with familial adenomatous polyposis or other diseases associated with multiple polyps of the gastrointestinal tract were excluded from the study.

<table>
<thead>
<tr>
<th>Curative surgery</th>
<th>Palliative surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1118; MPC n=213</td>
<td>n=382; MPC n=63</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre-metachronous MPC n=68</th>
<th>Synchronous MPC n=76</th>
<th>only Post-metachronous MPC n=64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-metachronous and synchronous MPC n=5</td>
<td>Synchronous and post-metachronous MPC n=10</td>
<td>All post-metachronous MPC n=83</td>
</tr>
<tr>
<td>Pre-metachronous and synchronous MPC n=32</td>
<td>Synchronous MPC n=28</td>
<td>Pre-metachronous and synchronous MPC n=3</td>
</tr>
<tr>
<td>Pre-metachronous MPC n=32</td>
<td>Synchronous MPC n=28</td>
<td>Pre-metachronous and synchronous MPC n=3</td>
</tr>
<tr>
<td>Pre-metachronous and synchronous MPC n=3</td>
<td>Synchronous MPC n=28</td>
<td>Pre-metachronous and synchronous MPC n=3</td>
</tr>
<tr>
<td>Pre-metachronous and synchronous MPC n=3</td>
<td>Synchronous MPC n=28</td>
<td>Pre-metachronous and synchronous MPC n=3</td>
</tr>
</tbody>
</table>

**FIGURE 1.**
OVERVIEW OF GROUPS OF PATIENTS WITH COLORECTAL CARCINOMAS
We analysed a variety of variables, i.e. age, gender, location of the index tumour, location of the second primary tumour, time of occurrence of the second primary neoplasm, and number of multiple primary neoplasms. We then calculated Kaplan-Meier survival curves and conducted log-rank tests for all patients who underwent curative intent surgery for their index tumour and had premetachronous, synchronous or postmetachronous second or third primary carcinomas. The median time of follow-up was 56 months.

All data were digitised for statistical analysis using Excel software and analysed using SPSS software (version 13.0). A p-value of less than 0.05 was considered statistically significant.

RESULTS

Of 1500 patients who underwent surgery for colorectal cancer, 276 patients (18.4%) had multiple primary carcinomas. In 194 cases (12.9% of 1500 patients and 70.2% of 276 patients), at least one carcinoma was detected outside the colon or rectum (extracolonic carcinomas).

Of the 1118 patients who underwent curative intent surgery, 213 patients (19%) developed multiple primary carcinomas. In 149 of these cases (70%), premetachronous or synchronous second primary tumours were detected.

A total of 1078 patients who underwent curative surgery for their index tumour and survived to hospital discharge were evaluated for the development of postmetachronous second primary carcinoma. Postmetachronous tumours were detected in 83 of these patients (7.7%) during the follow-up period.

The patients were divided into groups according to the time of occurrence of their multiple primary carcinomas and according to whether they had undergone curative or palliative surgery for their index tumour (Figure 1). These groups provided the basis for further statistical analyses.

Premetachronous multiple primary carcinomas

A total of 68 patients who underwent curative surgery for their index tumour had premetachronous multiple primary tumours. These patients included 43 women (63%) and 25 men (37%). The age of the patients at the time of occurrence of the index tumour ranged from 45 to 89 years (mean age: 69.7 years).

The index tumour was detected in the colon in 49 cases (72%) and in the rectum in 19 cases (27.9%). The second primary carcinoma was located in the colorectum in 8 patients (11.8%), outside the colorectum in 58 cases (85.3%) and both in and outside the colorectum in 2 patients.

Extracolonic carcinomas were mainly detected in the genital region (n=19, 27.9%) followed by the breast (n=18, 26.5%), kidney (n=3), urinary bladder (n=3) and other organs (n=13).

Premetachronous primary carcinomas occurred 1 to 31 years before surgery for the index tumour (mean time: 8.88 years). They were detected within 4 years prior to the

| TABLE 1 | SURVIVAL AND TIME OF OCCURRENCE OF MULTIPLE PRIMARY CARCINOMAS |
|----------|-----------------|-----------------|-----------------|-----------------|
| Time of occurrence | No of patients | Five-year survival rate | Ten-year survival rate | Median survival rate |
| No multiple primary carcinoma | 937 | 70% | 54% | 142 months |
| Premetachronous | 57 | 66% | 51% | 129 months |
| Synchronous | 60 | 72% | 58% | 133 months |
| Postmetachronous | 64 | 66% | 38% | 82 months |

Premetachronous versus synchronous carcinomas: p=0.526; premetachronous versus postmetachronous carcinomas: p=0.668; synchronous versus postmetachronous carcinomas: p=0.221

| TABLE 2 | SURVIVAL AND TIME OF OCCURRENCE OF PREMETACHRONOUS CARCINOMAS (<4 YEARS, 4-10 YEARS, >10 YEARS) |
|----------|-----------------|-----------------|-----------------|-----------------|
| Time interval between premetachronous and index tumours | No of patients | Five-year survival rate | Five-year survival rate | Median survival rate |
| < 4 years | 29 | 64% | 54% | 139 months |
| 4-10 years | 15 | 71% | 49% | 72 months |
| > 10 years | 22 | 75% | 63% | 129 months |

Less than 4 years versus 4 to 10 years: p=0.943; 4-10 years versus more than 10 years: p=0.880; less than 4 years versus more than 10 years: p=0.957
index tumour in 29 patients (44%), between 4 and 10 years before the index tumour in 15 patients (23%), and more than 10 years earlier in 22 patients (33%). All pre-metachronous carcinomas were treated with curative intent.

Synchronous multiple primary carcinomas

Seventy-six patients (6.8%) had further carcinomas that were diagnosed during the same period as the index carcinoma. The group of patients with synchronous carcinomas consisted of 53 men (70%) and 23 women (30%), aged from 37 to 88 years (mean age: 67.3 years). The index tumour was detected in the colon in 47 patients (61.8%) and in the rectum in 12 patients (15.8%). In 17 cases (22.4%), the index tumours were double tumours of the colon and rectum. Synchronous double carcinomas were discovered in the colorectum of 48 patients (63.2%) and in other organs in 28 patients (36.8%).

Extracolonic carcinomas were detected in the genital region (n=3), kidney (n=3), bladder (n=3), pancreas (n=3), stomach (n=3) and other organs (n=13). Surgery for synchronous second primary carcinomas was performed with curative intent in 95% (n=72) and with palliative intent in 5% (n=4).

### TABLE 3

<table>
<thead>
<tr>
<th>Location of the index tumour in the colon*</th>
<th>No of patients</th>
<th>Five year survival</th>
<th>Ten year survival</th>
<th>Median survival time</th>
</tr>
</thead>
<tbody>
<tr>
<td>No second primary carcinoma</td>
<td>498</td>
<td>69%</td>
<td>54%</td>
<td>140 months</td>
</tr>
<tr>
<td>Premetachronous</td>
<td>48</td>
<td>72%</td>
<td>64%</td>
<td>-</td>
</tr>
<tr>
<td>Synchronous</td>
<td>42</td>
<td>75%</td>
<td>61%</td>
<td>140 months</td>
</tr>
<tr>
<td>Postmetachronous</td>
<td>55</td>
<td>66%</td>
<td>45%</td>
<td>140 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of the index tumour in the rectum**</th>
<th>No of patients</th>
<th>Five year survival</th>
<th>Ten year survival</th>
<th>Median survival time</th>
</tr>
</thead>
<tbody>
<tr>
<td>No second primary carcinoma</td>
<td>439</td>
<td>72%</td>
<td>54%</td>
<td>145 months</td>
</tr>
<tr>
<td>Premetachronous</td>
<td>18</td>
<td>58%</td>
<td>33%</td>
<td>69 months</td>
</tr>
<tr>
<td>Synchronous</td>
<td>12</td>
<td>65%</td>
<td>65%</td>
<td>-</td>
</tr>
<tr>
<td>Postmetachronous</td>
<td>26</td>
<td>73%</td>
<td>43%</td>
<td>129 months</td>
</tr>
</tbody>
</table>

*No second primary versus premetachronous colon carcinomas: p=0.606; no second primary versus synchronous colon carcinomas: p=0.562; premetachronous colon carcinomas versus synchronous colon carcinoma: p=0.997.

**No second primary versus premetachronous rectum carcinomas: p=0.058; no second primary versus synchronous rectum carcinomas: p=0.983; premetachronous rectum carcinomas versus synchronous rectum carcinomas: 0.297

### TABLE 4

<table>
<thead>
<tr>
<th>Location of the index tumour in the colon or rectum</th>
<th>No of patients</th>
<th>Five year survival</th>
<th>Ten year survival</th>
<th>Median survival time</th>
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</thead>
<tbody>
<tr>
<td>Premetachronous</td>
<td>7</td>
<td>64%</td>
<td>64%</td>
<td>-</td>
</tr>
<tr>
<td>Synchronous</td>
<td>43</td>
<td>76%</td>
<td>76%</td>
<td>-</td>
</tr>
<tr>
<td>Postmetachronous</td>
<td>17</td>
<td>76%</td>
<td>40%</td>
<td>111 months</td>
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</table>

<table>
<thead>
<tr>
<th>Extracolonic location of multiple primary carcinomas</th>
<th>No of patients</th>
<th>Five year survival</th>
<th>Ten year survival</th>
<th>Median survival time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premetachronous</td>
<td>57</td>
<td>70%</td>
<td>54%</td>
<td>129 months</td>
</tr>
<tr>
<td>Synchronous</td>
<td>26</td>
<td>68%</td>
<td>49%</td>
<td>114 months</td>
</tr>
<tr>
<td>Postmetachronous</td>
<td>66</td>
<td>68%</td>
<td>46%</td>
<td>101 months</td>
</tr>
</tbody>
</table>
Postmetachronous multiple primary carcinomas

Postmetachronous second primary tumours were detected in 83 of a total of 1078 patients (7.7%). Of these, 64 patients (6%) did not have additional premetachronous or synchronous multiple primary carcinomas. Diagnosis was made between 3 and 159 months (mean time: 38.9 months) after curative surgery for the index tumour. The group of patients with postmetachronous carcinomas consisted of 46 men (55.4%) and 37 women (44.6%), aged from 43 to 86 years (mean age: 67.7 years).

The index tumour was detected in the colon in 55 patients (66.3%) and in the rectum in 26 patients (31.3%). In 2 cases (2.4%), the index tumours were double tumours of the colon and rectum.

Double primary carcinomas were discovered in the colorectum in 16 patients (19.2%), in other organs in 66 patients (79.5%), and in the colon and another organ in 1 patient (1.2%).

Extracolonic carcinomas were mainly located in the genital region (n=12) and in the lung (n=11) followed by the breast (n=10), bladder (n=5), stomach (n=5), kidney (n=4), liver (n=3), and other organs (n=17). Postmetachronous carcinomas were treated surgically with curative intent (R0 resection) in 68 of 83 cases (81.9%) and with palliative intent in 15 of 83 cases (18.1%).

Survival according to different variables

Deaths within 30 days of surgery were excluded from the calculation of survival. A total of 3% of the patients (2 of 68 patients) with premetachronous carcinomas and 8% of the patients (6 of 76 patients) with synchronous carcinomas died within 30 days of surgery.

First, we constructed survival curves for patients with and without multiple primary carcinomas in relation to the time of tumour occurrence (premetachronous, synchronous and postmetachronous carcinomas). There were no significant differences between the groups (Table 1).

The survival of patients with premetachronous carcinomas was also calculated according to the time interval between the multiple primary and index cancers. For this purpose, the patients were divided into three groups: patients with a tumour-free interval between the premetachronous and index tumours of more than 10 years, 4 to 10 years, and less than 4 years. No significant differences between these groups were detected (Table 2).

We then compared patient groups depending on the location (colon or rectum) of the index tumour that was treated surgically with curative intent. There were no significant differences between the groups (Tables 3).

Patient groups were also compared according to the location (intracolonic or extracolonic) of the multiple primary carcinomas. No significant differences in survival were detected (Tables 4).

In a further analysis, we compared the survival of patients younger than 60 years and the survival of patients older than 60 years within the various groups (patients without second primaries and patients with synchronous, premetachronous or postmetachronous multiple primary carcinomas).

No significant differences were found in the groups of patients with double primary tumours. Only in the group of patients without second primaries did patients who were older than 60 years have longer survival than those who were aged less than 60 years (p<0.001).

DISCUSSION

In the past, several authors reported that the incidence of multiple primary carcinomas continues to increase. The reasons for this are a longer life expectancy, an increasing number of curatively treated patients, and improved diagnostic methods during screening procedures. The overall incidence of multiple primary cancers of the colorectum and other organs is reported to range from 0.83% to 10%.9,10

Whereas many studies focus on the location of multiple primary carcinomas, the time interval between first and second primary tumours and the number of carcinomas were rarely discussed. A Spanish study, the number of carcinomas and the time interval between diagnoses did not play a role in prognosis. Pan et al., Bekdash et al found that the longer the interval between two malignant tumours, the better the prognosis.12

There is a paucity of literature addressing the question of whether and, if so, to what extent the presence of a second or third primary carcinoma has a prognostic role and whether the presence of multiple primary tumours must be considered an independent prognostic factor in the treatment of colorectal cancer.

Locations of the index tumour and the second primary carcinoma

Available studies reached different conclusions about the role of the location of the index tumour in the risk of developing a second primary carcinoma. Gervaz et al., for example, reported that patients had a higher risk of developing a second primary carcinoma if their index tumour was located in the colon. By contrast, Maruyama et al. found that multiple primary carcinomas were more common among patients with rectal carcinomas.

In our patient population, second primary tumours were detected more often in patients with cancer of the colon than in patients with cancer of the rectum. A comparison of these groups however, did not reveal significant differences in the development of second primary tumours or survival.

There are also several studies addressing the location of second primary malignant tumours (colorectal versus extracolonic carcinomas).

In different studies, multiple primary carcinomas were located in the colorectum in 43-57% of the patients with a colorectal index tumour. In our patient population there was only a high percentage of colorectal second primary carcinomas in the group of patients with synchronous double primary carcinomas (64.5%).
In our patient population there were no significant differences in survival time for the variable "Location of the second primary carcinoma: colorectum versus other organs." The site of the second primary cancer is thus not an independent prognostic factor in patients with multiple carcinomas.

**Time of occurrence of multiple primary carcinomas**

**Premetachronous carcinomas**

In the literature, the time interval between premetachronous second primary malignancies and colorectal tumours ranges from 1 to 39 years.\(^{17,18}\)

In our study, the interval between premetachronous double primary carcinomas and the index tumour was similar to that reported in the literature. The mean interval was 8.9 years. It is unclear, however, to what extent the duration of this time interval influences prognosis.

We divided the patients of our population into three groups depending on whether the time interval between the premetachronous carcinoma and the index tumour was less than 4 years (n=29), 4 to 10 years (n=15), and more than 10 years (n=22). A comparison of survival times, however, did not show significant differences. There was thus no advantage of longer or shorter time intervals between the occurrence of the second primary malignancy and the index carcinoma. As a result, the time interval between a premetachronous second primary malignant tumour and a colorectal carcinoma is not an independent prognostic factor.

**Synchronous carcinomas**

The survival rates for patients with a single colorectal malignant tumour in comparison with patients with synchronous second carcinomas vary in the literature. Some authors reported a similarly good prognosis for patients with a single colorectal carcinoma and patients with synchronous carcinomas.\(^{19}\) In older studies, however, prognosis was sometimes found to be poorer in patients with synchronous carcinomas.\(^{20}\) In our study, the five-year survival rate was 72% among patients with synchronous second primary carcinomas and 70% among patients with a single colorectal carcinoma. The ten-year survival rate was 58% among patients with synchronous carcinomas and 54% among patients with a single colorectal carcinoma. These results correspond to those reported in the majority of current studies on this tumour entity. Since there was no significant difference between patients with synchronous carcinomas and those with a single colorectal carcinoma, synchronous occurrence is not an independent prognostic factor.

**Metachronous carcinomas**

The literature provides different results concerning the prognosis of patients with metachronous second primary cancers when compared to those with synchronous second malignancies. Some authors report a better outcome for patients with metachronous tumours,\(^{21}\) other authors found lower\(^{22}\) or similar survival rates.\(^{23}\)

In our patient population, patients with premetachronous and postmetachronous double primary carcinomas showed similar survival rates. Their prognosis was not different from that of patients with a single colorectal carcinoma and patients with synchronous second primary carcinomas.

**Number of multiple primary carcinomas**

Approximately 6.9-13.6% of the patients with multiple primary carcinomas develop a third primary carcinoma.\(^{24}\) In our own patient population, 19% of the patients (39 of 205 patients) with multiple primary carcinomas had a third primary malignancy. The incidence was thus considerably higher than that reported in the literature.

These patients had a five-year survival rate of 74% and a median survival time of 151 months. These results are similar to those of patients with a single colorectal carcinoma who had a five-year survival rate of 71% and a median survival time of 167 months or patients with two primary malignancies (69%, 112 months). There was thus no evidence that the presence of third primary carcinomas influences prognosis.

**Follow-up and outlook**

Since the incidence of multiple primary carcinomas has been increasing in recent years, particular attention should be paid to the follow-up of tumour patients. Colonoscopy should therefore be recommended for risk patients even after the end of the five-year period. If diagnosed at an early stage, usually by endoscopy, colorectal second primary carcinomas can be treated surgically with curative intent.

Since colorectal carcinomas are often combined with gynaecological and urological second primary malignancies, patients with gynaecological or urological malignancies should be screened for colorectal carcinoma at history taking.\(^{25}\) Clinical studies, however, must be conducted in order to assess the efficiency of an extended follow-up programme.

In summary, for the population of patients who were treated at the University Hospital of Luebeck, prognosis was not influenced by either the location (colorectal or extracolonic multiple primary carcinomas), the time of occurrence (premetachronous, synchronous or postmetachronous multiple primary carcinomas) or the number of multiple primary carcinomas.

As a result, the presence of multiple primary carcinomas does not generally worsen the prognosis of patients with colorectal cancer. Although many authors and research projects have addressed the characteristics of multiple carcinomas and have offered some insight into the genesis of these tumours, many questions are still unanswered. Epidemiological, clinical and molecular genetic studies should be conducted in order to help us better understand the genesis of multiple carcinomas.
Influence of second or multiple tumors on the prognosis of patients with colorectal cancer

SUMMARY

UTICAJ DRUGOG ILI MULTIPLIH TUMORA NA PROGNOZU IZLEČENJA BOLESNIKA SA KOLOREKITALNIM KARCINOMOM

Uvod: Kolorektalni karcinom je jedan od najčešćih karcinoma u zemaljama Zapadne Evrope za koga je do sada identifikovano više prognoških faktora. U literaturi, malo studija obraduje uticaj multipulnih primarnih karcinoma na prognozu lečenja. Ova studija ispituje uticaj drugog ili multipulnih primarnih tumora na prognozu bolesnika sa kolorektalnim karcinomom.


Rezultati: Nije ustanovljena statistički značajna razlika u preživljavanju između bolesnika u pojedinim grupama niti između bolesnika sa i bez multipulnih primarnih tumora.

Zaključak: Prisustvo multipulnih karcinoma nije nezavisni prognoški faktor kod bolesnika sa kolorektalnim karcinomom. Bolesnike sa multipulnim primarnim tumorima ne karakteriše lošija prognoza i ova bolesnike treba kurativno hirurški lečiti i pružiti im odgovarajuću postoperativnu negu.

Ključne reči: kolorektalni karcinom, multipli primarni karcinom, prognoški faktor

REFERENCES

