Liver metastases are diagnosed synchronously with the primary tumour in 25% of patients with colorectal cancer. A half of the remaining patients develop liver metastases within 3 years following colectomy. At present, the only radical treatment of metastases is liver resection. Only 2.6% of patients survive 3 years if such treatment is not implemented.

The aim of the study was to assess predictive factors of long-term survival in the group of patients with unresectable colorectal liver metastases carcinoma.

Material and methods. Of 1029 patients with colorectal liver metastases, who were treated in the Department of General, Transplant and Liver Surgery of the Medical University of Warsaw in the years 2006-2012, cases of liver metastases assessed intraoperatively as unresectable were selected. The retrospective analysis included 85 patients. Based on the medical documentation, information concerning age, sex, characteristics of primary and secondary tumours, reasons for unresectability, neoadjuvant chemotherapy as well as local treatment of liver tumours was collected. Preoperative serum concentrations of CEA and CA 19-9 markers were considered. The Cox regression model, Kaplan-Meier estimator and log-rank test were applied in the statistical analyses.

Results. The most common reason for unresectability were: number of metastases in 31 patients (36.5%) and extrahepatic metastases in 19 cases (22.4%). Overall survival in the entire group was 56.1% and 15.5% after 1 and 3 years respectively. A single-factor analysis showed that CEA serum levels (p=0.032; HR=1.002 per increase by 1 ng/ml) and the presence of extrahepatic metastases (p=0.037; HR=2.06) were predictors of worse survival. In a multivariate analysis, CEA concentration (p=0.017; HR=1.002 per increase by 1 ng/ml) was an independent predictor of death whereas the presence of extrahepatic metastases were not statistically significant (p=0.059; HR=2.09).

Conclusions. Serum concentration of CEA marker is an independent predictor of worse survival, but the presence of extrahepatic metastases shows a similar tendency.

Liver metastases are diagnosed synchronously with colorectal cancer in as many as 25% of patients. Over 23% of them also present extrahepatic metastases. Nearly a half of the remaining patients develop metachronous liver metastases within 3 years following bowel resection (1, 2).

Unfortunately, only 10-25% of patients with colorectal liver metastases are qualified to radical surgical treatment (2, 3). Metastatic tumours in the remaining patients are considered unresectable, mainly due to their dissemination in both liver lobes, presence of extrahepatic metastases or the inability to preserve an adequate future liver remnant volume. In such patients, palliative treatment is implemented, such as chemotherapy, thermoablative metastases or selective internal radiotherapy (SIR-spheres). Apart from relieving symptoms and prolonging survival, chemotherapy may enable qualification of patients with primarily unresectable liver metastases to resection (downsizing). Adam et al. report that this is possible in approximately 12.5% of
According to Stangl et al., overall survival of patients with colorectal liver metastases in whom no treatment is implemented amounts to 31.3%, 7.9% and 2.6% following one year, 2 years and 3 years of diagnosis respectively (4). Radical surgical treatment in combination with chemotherapy prolongs survival even to 58% after 5 years of resection (5). If metastases are considered unresectable, palliative treatment in the form of chemotherapy and local thermoablation is characterised by 5-year survival of 10% and 17% respectively (6, 7). Application of selective internal radiotherapy is indicated only if metastases are limited to the liver when there is no response to chemotherapy (8). In patients with unresectable synchronous metastases, primary tumour resection increases the survival median by 10 months as against a situation in which resection is not performed (9).

Attempts to identify predictive factors of worse survival of patients after liver resection due to colorectal metastases were undertaken on numerous occasions (1, 10-13). The common factors are: advancement of the primary tumour, number and size of metastases, serum concentration of carcino-embryonic antigen (CEA), time between diagnosis of metastases and resection of the primary tumour and presence of metastatic tumours beyond the liver. Patients with unresectable metastatic tumours are characterised by worse survival, but there are no reports concerning predictive factors in this group.

The aim of the study was to specify predictive factors of long-term survival in the group of patients with unresectable colorectal liver metastases.

MATERIAL AND METHODS

1029 patients with colorectal liver metastases were treated in the Department of General, Transplant and Liver Surgery of the Medical University of Warsaw in 2006-2012. A retrospective analysis was conducted in the group of 85 patients (8.6%) in whom laparotomy was performed with the intention of resection, but intraoperatively metastases were assessed as unresectable. The group comprised 61 (71.8%) men and the median age was 61 years (range from 29-91).

The causes for unresectability were specified on the basis of the documentation available. The analysis included the following variables: age, sex, location of primary and secondary tumours, time of diagnosing metastases in relation to the primary tumour resection, application of neoadjuvant chemotherapy, local thermoablation, presence of extrahepatic metastases and preoperative serum concentration of CEA and CA 19-9 markers. Overall survival was defined as time that passed from laparotomy to patient’s death.

In order to specify risk factors of worse survival in the examined group, a range of single-factor analyses were performed with the use of the Cox proportional hazard model. Statistically significant variables were included in the multivariate model. Hazard ratios are signified with HR acronym. 95% confidence intervals for hazard ratios are presented in brackets and signified with 95% CI. The level of statistical significance was p<0.05. The calculations were performed in a STATISTICA 10 system (StatSoft Inc, Tulsa, USA).

Survival was calculated with the use of the Kaplan-Meier estimator. The log-rank test was also used for comparison of the survival in groups exposed to selected risk factors.

RESULTS

The most common causes of unresectability were: number of metastases (36.5%) and presence of extrahepatic metastases (22.4%) (tab. 1). Neoadjuvant chemotherapy was applied in 33 patients (55.9%) and intraoperative thermoablation was performed in 12 cases (20.3%). The primary tumor was localised in the rectum in 20 patients (33.9%). In

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Number of metastases</td>
<td>31</td>
<td>36.5</td>
</tr>
<tr>
<td>Presence of extrahepatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>metastases</td>
<td>19</td>
<td>22.4</td>
</tr>
<tr>
<td>Location near large vessels</td>
<td>16</td>
<td>18.8</td>
</tr>
<tr>
<td>Tumour size</td>
<td>10</td>
<td>11.8</td>
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<tr>
<td>Other</td>
<td>9</td>
<td>10.5</td>
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</table>
20 cases (33.9%), metastases were synchronous, in 45 patients (76.3%) tumours were present in both lobes of the liver, and in 18 patients (30.5%), metastases were also found beyond the liver. The median values of preoperative serum concentrations of CEA and CA 19-9 markers amounted to 28.8 ng/ml (range: 1-1204 ng/ml) and 57.7 U/ml (range: 0.6-4774 U/ml) respectively.

Overall one- and three-year survival in the entire group was 56.1% and 15.5% respectively (fig. 1). The longest follow-up period equalled 51 months. Therefore, estimation of 4-year survival was possible – it was 10.7%.

The single-factor analyses indicated that two variables affected overall survival in the examined group. These were: presence of extrahepatic metastases (p=0.037; HR=2.06; 95% CI 1.05-4.05) and preoperative serum CEA level (p=0.032; HR=1.002 per increase by 1 ng/ml; 95% CI 1.0001-1.003 per increase by 1 ng/ml) (tab. 2). The multivariate analysis revealed that preoperative serum CEA level (p=0.017; HR=1.002 per increase by 1 ng/ml; 95% CI 1.001-1.003 per increase by 1 ng/ml) was the independent risk factor of death whereas the presence of extrahepatic metastases (p=0.059; HR=2.09; 95% CI 0.97-4.15) placed itself slightly above the level of statistical significance (tab. 2).

When comparing survival prediction including the two aforementioned factors, the examined population was divided into 4 groups (fig. 2). In the case of preoperative serum CEA level, the 100 ng/ml cutoff was assumed arbitrarily, based on the literature, and thus the groups of patients with the result >100 ng/ml and ≤100 ng/ml were distinguished. The groups distinguished were as follows: group 1 – no extrahepatic metastases and CEA ≤100 ng/ml; group 2 – no extrahepatic metastases and CEA >100 ng/ml; group 3 – extrahepatic metastases and CEA ≤100 ng/ml and group 4 – extrahepatic metastases and CEA >100 ng/ml. Statistically significant differences in survival of patients in these 4 groups were observed (p=0.028).

**DISCUSSION**

Currently, the possibility of resecting colorectal liver metastases is determined based on the assessment of the future liver remnant.
volume. Therefore, resectability is sometimes defined as the possibility of obtaining oncological radicality of the resection while preserving two adjacent liver segments, maintaining appropriate inflow and outflow as well as drainage of bile and preserving an adequate future liver remnant volume (at least 20% of the total liver volume) (14). If there are features of parenchymal damage following chemotheraphy, this amount should be greater. A high number of tumours and the size of the tumour are not contraindications themselves, but they may result in a failure to meet the resectability criteria that result from the definition. However, preoperative systemic chemotherapy is recommended when there are >4 metastases to the liver, even if resectability criteria are met (15). Considering other additional extrahepatic metastases, satisfactory survival is obtained in patients after radical resection of lung metastases (16). In patients with intra-abdominal metastases (e.g. to the lymph nodes or peritoneum), satisfactory outcomes of combined resection of hepatic and extrahepatic lesions are achieved in selected patients only (17).

The assessment of resectability prior to laparotomy may still be challenging despite advanced imaging techniques. Even high-resolution, contrast-enhanced computed tomodography is characterised by the sensitivity of 80-87%, which means that accurate assessment of the extent of lesions in the remaining group may be performed only intraoperatively (18). The literature reports that unresectability of metastases is diagnosed during laparotomy in 7.7-70% of patients, and in the latest reports, this percentage amounts to 15% (19-23).

In this study, unresectability of metastases was identified during laparotomy in 8.6% of patients. Performing laparotomy in patients who do not qualify for resection exposes them to pain, risk of complications, longer hospitalisation and frequently, also causes delayed implementation of chemotherapy. In order to avoid such situations, it is attempted to apply prediction models for unresectability of lesions or conduct exploratory laparoscopy. However, a decrease in the number of patients who are disqualified from resection is rather associated with extending the limits of resectability, particularly in patients with extrahepatic metastases. In the material presented herein, extrahepatic metastases were the cause of disqualification in 19 cases (22.4%), i.e. 1.8% of all patients treated due to liver metastases from colorectal carcinoma.

In the literature, there are few reports concerning survival prediction in patients who underwent solely laparotomy despite the intention of performing liver resection. Bennett et al. present a group of patients with unresectable metastases where 3- and 5-year survival was 5% and 0% respectively (20). In the analysis presented above, the respective values of 3- and 5-year survival were 15.5% and 0%. The difference in the three-year survival may be associated with relatively small groups based on which the survival was estimated. Older reports concerning patients with metastases to the liver in whom no treatment is implemented show that 5-year survival amounts to 2% (4, 24) and thus is comparable to the contemporary results. It demonstrates that radical surgical treatment is still the basic treatment that brings satisfactory outcomes.

In predicting survival of patients after resection of colorectal liver metastases, numerous clinical and pathological as well as molecular factors are used (1, 10-13, 25, 26). The most commonly listed factors included in the first group are: primary tumour stage, preoperative serum CEA concentration, size and
number of metastatic lesions, time between diagnosing metastases and resection of the primary tumour, presence of extrahepatic metastases or size of the preserved margin during resection. Based on these data, scales of survival have been created, the most widely acknowledged of which are the ones described by Fong et al. and Iwatsuki et al. (1, 10).

An attempt to predict survival of patients with unresectable metastases to the liver has been undertaken in few studies (20, 27, 28). In this group of patients, the predictors of worse survival were: number of metastases >10, presence of lung metastases, peritoneal involvement and serum CEA or CA 19-9 concentration. The analysis presented above also demonstrates the predictive value of CEA concentration and extrahepatic metastases (tab. 2 and fig. 2) despite no statistical significance of the latter in the multivariate analysis.

CONCLUSIONS

Perhaps the stratification of patients with unresectable colorectal liver metastases will, in the future, enable identification of patients in whom even more aggressive treatment may be recommended in hope of obtaining satisfactory outcomes. To make this possible, however, we need analyses conducted among larger groups of patients so as to confirm or refuse predictive values of the aforementioned factors. The analysis presented above indicates that serum concentration of CEA marker is an independent predictor of worse survival, but the presence of extrahepatic metastases shows a similar tendency. The results of this study and other similar analyses may also occur useful for providing information to the patients concerning prognosis if radical treatment cannot be implemented.

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