Acta Oncologica 27 (1988) Fasc. 1

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SURVIVAL AFTER PALLIATIVE RADIOTHERAPY OF LIVER METASTASES

A search for prognostic factors

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Abstract

Seventy-nine patients, aged 21–79 years, were given mega-voltage radiotherapy for symptomatic liver metastases from various primary malignancies. The material was analysed with respect to survival and ability to complete treatment as planned. All patients died. Median survival from start of radiotherapy was 4 months (1 month–2.5 years). Multivariate survival analyses selected only low or high leukocyte count ($<4\times10^9$/l or $>10\times10^9$/l) as significant prognostic factors indicating short survival. Other clinical and biochemical parameters including liver function tests were not correlated to survival. Multivariate logistic regression analyses of the ability to complete treatment showed that patients with mammary cancer and thrombocyte count $<100\times10^9$/l were less likely to complete the radiotherapy. We conclude that less time-consuming methods of palliation should be tried for these patients as survival time is rather limited in patients with symptomatic liver metastases.

Key words: Liver neoplasms; metastases, radiotherapy, prognostic factors, leukocytes, thrombocytes, liver function tests.

The diagnosis of hepatic metastases usually indicates a very poor prognosis with an overall median survival in untreated patients in the range of 2–3 months (1, 10, 12). Some studies indicate a palliative effect of liver irradiation (2, 14). As the survival is so limited and the treatment effects uncertain, this study was made in an attempt to describe high risk patients with respect to survival and ability to complete the radiotherapy.

Material and Methods

This follow-up study includes 79 consecutive patients given mega-voltage radiotherapy for liver metastases during the period January 1st 1976 to December 31st 1984. Patients' characteristics at the start of radiotherapy were collected from the medical records. There were 41 men and 38 women with an age ranging from 21 to 79 years (mean age 52). The primaries were cancer of the breast (n=27), gastrointestinal tract (n=16), lung (n=11), lymphoma (n=10) and testis (n=6). Other primaries accounted for 9 cases. Most of the patients had massive metastatic disease involving both liver lobes but a more exact extent of liver involvement could not be determined in this follow-up study. Seventy-six patients had one or more symptoms requiring palliative treatment. The patients had received a variable amount of chemotherapy earlier in the course of their disease. All cytostatic treatment was discontinued when hepatic radiotherapy was started.

Most of the patients received a total dose of 20 Gy with 1–2 Gy per fraction. Radiotherapy lasted 1–67 days (mean 18 days). Mean CRE value was 691 reu (120–1540 reu). The majority of the cases were irradiated through opposing AP-fields covering the entire liver region. In cases with major tumor involvement of the portal area only, treatment was given from a smaller field including the portal region. Most patients were given corticosteroids concomitantly.

The material was analysed with respect to ability to complete treatment as planned and survival from start of radiotherapy. As this patient population was heterogeneous in several aspects, possible differences of all continuous variables between the primary cancer groups were explored with analyses of variance (5). The following variables were tested in both univariate and multivariate analyses: age, sex, site of primary tumor, interval from primary diagnosis to start of radiotherapy for liver metastasis, reason to give radiotherapy and results of

Accepted for publication 21 August 1987.

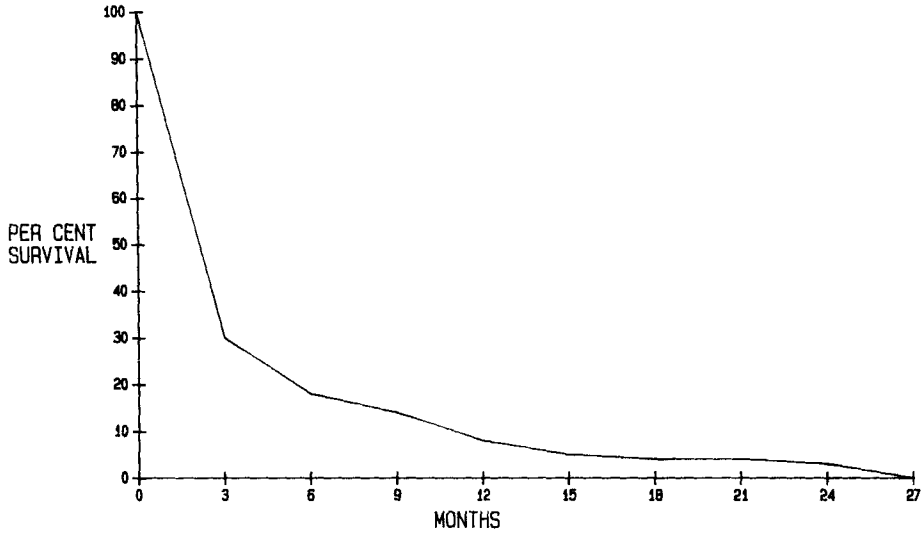

Figure. Survival after radiotherapy of liver metastases.

laboratory tests given in the Table. All continuous variables were divided into 3 groups defined by cutpoints at the 25th and 75th percentiles to look for trends in survival. Survival curves were calculated with the life-table mehod (4) and differences between survival curves tested with the log rank test (5). Multivariate survival analyses were performed with Cox's regression model (3). Stepwise logistic regression (6) was used to relate possible explanatory variables to an event of interest (i.e. ability to complete treatment). All statistical analyses were performed with the BMDP statistical software package (5).

Table

Laboratory results tested in multivariate analysis

Variable	Lowest	Median	Highest
Hemoglobin, g/dl	7.3	11.5	15.7
Erythrocyte sedimentation rate, mm/h	2	55	140
Leukocytes $\times 10^9$/l	1.1	7.2	243
Thrombocytes $\times 10^9$/l	13	255	792
Lactate dehydrogenase, U/l	235	960	7 505
Alkaline phosphatase, U/l	173	919	5 900
Gamma glutamyl transferase, U/l	22	380	3 591
Alanine aminotransferase, U/l	9	64	587

Results

Twenty-nine of 79 patients were unable to complete treatment as planned. In 25 of these patients the clinical state deteriorated rapidly either as a result of progressive disease, or due to side effects of treatment (mainly gastrointestinal). In four patients treatment was stopped because of leuko- or thrombocytopenia. Multivariate logistic regression analyses of ability to complete radiotherapy as planned, showed that patients with mammary carcinoma and low thrombocyte count ($<100\times10^9$/l) were less likely to complete the radiotherapy ($p<0.01$).

The interval from primary diagnosis to start of therapy for liver metastases, age, thrombocyte count and gamma glutamyl transferase had significantly different mean values in the patients with different primaries (analyses of variance). Patients with mammary carcinoma had the lowest mean thrombocyte count (190×10^9/l vs. 302×10^9/l in the rest of the patients) and highest mean gamma glutamyl transferase (1 020 U/l vs. 398 U/l). Leukocytosis was not associated with any particular diagnosis.

All patients died, and their survival ranged from less than 1 month to 2.5 years. The median survival was 4 months (Figure). In univariate survival analyses only thrombocytopenia (thrombocyte count $<100\times10^9$/l), leukopenia (white blood cell count $<4\times10^9$/l) or leukocytosis (white blood cell count $>10\times10^9$/l) were significant prognostic factors ($p<0.05$). Multivariate survival analyses with the variable leukocyte count transformed (reference leukocyte counts $4.0–10.0\times10^9$/l coded as 0 and leukopenia or leukocytosis coded as 1 confirmed low leukocyte count or leukocytosis to be the only significant prognostic factors (regression coefficient 0.51, SE 0.24). If all other continuous variables were divided into 2 groups with cutpoint at the 25th (hemoglobin) or 75th percentile (other variables) and included in a multivariate survival analysis, no new significant prognostic factors with respect to survival were identified. In particular, there was no correlation between survival and liver function tests.

Discussion

Low thrombocyte and leukocyte count were significant prognostic factors with respect to ability to complete treatment and survival respectively. Both leuko- and

thrombocytopenia in patients with advanced cancer probably indicate bone marrow failure due to advanced disease and/or, especially, earlier extensive treatment with myelotoxic drugs. Thrombo- or leukocytopenia has not to our knowledge been reported earlier as prognostic factors in patients with liver metastases. Leukocytosis also indicated high risk patients with short survival. Similar observations have been reported in a study of patients with liver metastases from colorectal cancer (7).

Trying to identify prognostic factors in multivariate analyses by considering p-values only may be misleading (13). This was confirmed in the present study as leukocyte count used as a single continuous variable in the multivariate survival analyses was not significantly correlated to survival (p-value 0.8). The model structure of the Cox's analysis then indicated a low leukocyte count as a low-risk factor and high leukocyte count as a high-risk factor. The proportional assumption of the Cox's model as tested with plot was, however, only satisfied after recoding both low and high leukocyte counts into a single category. This emphasizes the importance of not using variables such as results of laboratory tests in the continuous form only. Setting threshold in a continuous variable such as leukocyte count is difficult. We selected leukocytes <4 and $>10\times10^9$/l as this grouping gave reasonable numbers of patients (9 and 18 patients) and was close to reference limits.

Contrary to the present results and those of FORTNER et coll. (8, 9) most authors (1, 2, 7, 10, 11) have found a positive correlation between various liver function tests (most often alkaline phosphatase and bilirubin) and survival. Most of the above cited work refer to patients with metastases in the liver from colorectal cancers only. Thus, the discrepancy in reports of liver function tests as prognostic factors may in part be due to differences in patient populations.

In this follow-up series the subjective response to hepatic radiotherapy could not be established in the majority of patients due to lack of information in the records. Though in a few patients the treatment clearly had a good palliative effect the benefit of hepatic radiotherapy remained questionable in most cases.

In conclusion, leukocyte count should be considered as a possible prognostic factor in patients with liver metastases from various primary malignancies treated with radiotherapy. As the median survival in these patients is less than 3 months, less time-consuming methods of palliation should be applied.

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