

Karnofsky Performance Score Is Predictive of Survival After Palliative Irradiation of Metastatic Bile Duct Cancer

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Abstract. *Background/Aim: Palliative irradiation is effective in alleviating symptoms in patients with metastatic cancer in general. However, little data exist regarding irradiation of metastatic bile duct cancer. Selection of the best regimen for such a patient should be based on their survival prognosis. Patients and Methods: This study included five patients irradiated for metastatic bile duct cancer and aimed to identify predictors of survival by analyzing six factors: age, gender, general condition (Karnofsky performance score), metastatic site receiving palliative irradiation, metastases outside irradiated sites and time between diagnosis of bile duct cancer and palliative irradiation. Results: In the whole series, median survival was 3 months. Survival rates at 3 and 6 months were 40% and 40%, respectively. A Karnofsky performance score >70% had a borderline significant association with better survival ($p=0.05$). Conclusion: Karnofsky performance score was identified as predictor of survival and should be considered when assigning the radiation regimen to patients with metastatic bile duct cancer.*

Patients with bile duct cancer frequently develop metastases over the course of their disease (1). In a retrospective study including 80 patients with bile duct cancer, 28% experienced distant metastases as first failure site after a median of 2 years' follow-up (2). Since metastatic bile duct cancer is a palliative situation, alleviation of symptoms and quality of life have priority rather than prolongation of life. Thus, for these patients, the time they receive treatment such as radiotherapy should be as short as reasonably possible. This applies particularly to those patients with a very limited

prognosis of a few weeks or very few months. However, some patients live longer and could benefit from longer-lasting irradiation regimens with higher total doses. According to previous studies of patients irradiated for brain metastases or metastatic compression of the spinal cord, higher doses resulted in better local control and survival in patients with more favorable survival prognoses (3, 4). These data show that it is very important to rate a patient's remaining lifespan in order to deliver the best possible therapy. Therefore, the present study was conducted aiming to identify factors helping to predict the survival time of patients irradiated for metastatic bile duct cancer.

Patients and Methods

Five patients irradiated for metastatic adenocarcinoma of the bile duct were included in this study and retrospectively evaluated. Six factors were analyzed for an association with survival: patient age (≤ 63 vs. >63 years, median of 63 years), gender, general condition [Karnofsky performance score (KPS) $\leq 70\%$ vs. $>70\%$], site of metastases receiving palliative irradiation (osseous vs. other), further metastases outside the irradiated sites (no vs. yes) and time between initial diagnosis of bile duct cancer and palliative irradiation (≤ 14 vs. >14 months, median of 14 months) (Table I).

Planned radiotherapy regimens were 3 Gy per fraction up to 30-36 Gy in four patients and 1.8 Gy per fraction up to 45 Gy in one patient. In two patients irradiated with 3 Gy per fraction, the planned total dose of 30 Gy was not reached and radiotherapy had to be stopped after 9 Gy due to disease-related worsening of their performance status. Survival was calculated from the first irradiation fraction with the Kaplan–Meier method and the log-rank-test (5). p -Values of less than 0.05 were considered significant.

Results

Considering the entire cohort, the median survival was 3 months. Survival rates at 3 and 6 months were 40% and 40%, respectively. On survival analysis, a KPS of $>70\%$ was borderline significantly associated with a better outcome ($p=0.05$). The results of the survival analysis are summarized in Table II.

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Table I. Factors analyzed for an association with survival after palliative irradiation for bile duct cancer.

Characteristic	No. of patients
Age at radiotherapy	
≤63 Years	3
>63 Years	2
Gender	
Female	3
Male	2
Karnofsky performance score	
≤70%	3
>70%	2
Site of metastases receiving palliative radiotherapy	
Osseous	3
Other	2
Further metastases outside irradiated sites	
No	1
Yes	4
Time between initial diagnosis and palliative irradiation	
≤14 Months	3
>14 Months	2

Table II. Survival rates at 3 and 6 months after palliative irradiation for bile duct cancer.

Characteristic	3 Months (%)	6 Months (%)	p-Value
Age at radiotherapy			
≤63 Years	33	33	
>63 Years	50	50	0.97
Gender			
Female	33	33	
Male	50	50	0.49
Karnofsky performance score			
≤70%	0	0	
>70%	100	100	0.05
Site of metastases receiving palliative radiotherapy			
Osseous	33	33	
Other	50	50	0.69
Further metastases outside irradiated sites			
No	100	100	
Yes	25	25	0.78
Time between initial diagnosis and palliative irradiation			
≤14 Months	67	67	
>14 Months	0	0	0.26

Discussion

The prognoses of most patients with metastatic bile duct cancer are poor and must be improved. The same applies to patients with locally advanced non-resectable disease. Therefore, clinical and preclinical studies have been performed carried to improve the prognoses of patients with locally advanced or metastatic bile duct cancer (6-9). However, no study focused on palliative irradiation of patients presenting with metastases from this type of cancer. Such studies would be quite important, particularly those performed to identify prognostic factors associated with survival. In principle, several irradiation regimes are available and used to treat patients with metastatic cancer. These regimens range from single fractions of 4-10 Gy to regimens with lower doses per fraction up to higher total doses that can take several weeks. The latter regimens should be limited to patients with a comparably good survival prognosis. Two studies have shown that longer-lasting regimens with higher total doses can result in better local control of the metastases and even in better survival in these patients (2, 3).

In a retrospective study published in 2012, 109 patients with a favorable survival prognosis being irradiated for brain metastases from various primary tumors with 30 Gy in 10 fractions over 2 weeks were compared to 75 patients irradiated for the same indication with 40 Gy in 20 fractions (2). The 1-year local control rates were 28% after 30 Gy and 44% after 40 Gy, respectively ($p=0.047$, obtained from the multivariate analysis). The 1-year survival rates were 50%

and 61%, respectively ($p=0.008$). In a matched pair analysis published in 2011, 191 patients with a favorable survival prognosis who received 30 Gy in 10 fractions over 2 weeks for metastatic compression of the spinal cord from different primary tumors were compared to 191 patients receiving 37.5 Gy in 15 fractions over 3 weeks or 40 Gy in 20 fractions over 4 weeks (3). The 2-year local control rates were 71% after 30 Gy compared to 92% after 37.5 Gy or 40 Gy ($p=0.012$). The 2-year survival rates were 53% and 68%, respectively ($p=0.032$).

In contrast, patients with less favorable survival prognoses irradiated for metastatic cancer did not benefit from longer radiation regimens with higher doses. This applied to both patients irradiated for brain metastases and those irradiated for spinal cord compression (10, 11). A retrospective study from 2007 including 442 patients treated with whole-brain irradiation for brain metastases showed that 20 Gy in five fractions over 1 week provided similar survival rates as 30 Gy in 10 fractions over 2 weeks (10). Six-month survival rates were 24% and 27% ($p=0.29$). In a recent randomized phase III trial of 203 patients irradiated for metastatic compression of the spinal cord, overall response rates of motor function ($p=0.73$), ambulatory rates following irradiation ($p=0.86$), 6-month local progression-free survival ($p=0.51$) and 6-month overall survival ($p=0.68$) were not significantly different after 30 Gy in 10 fractions over 2 weeks and 20 Gy in five fractions over 1 week (11).

Taking into account these data from the literature, it becomes obvious that palliative irradiation should always consider the patient's survival prognosis. Thus, to determine a patient's prognosis as accurately as possible is of great importance in order to avoid over- or undertreatment. In the present study that focused specifically on patients treated with palliative irradiation for metastatic bile duct cancer, the KPS showed a strong correlation with prognosis and could, therefore, guide physicians when they aim to select the best possible radiation regimen for an individual patient requiring palliative irradiation for metastases from bile duct cancer. Patients with a KPS of $\leq 70\%$ should be irradiated with a less time-consuming regimen such as 20 Gy in five fractions over 1 week, whereas patients with a KPS of $>70\%$ are more appropriately treated with a longer-lasting regimen providing a higher radiation dose such as 30 Gy in 10 fractions over 2 weeks or even 40 Gy in 20 fractions over 4 weeks.

In conclusion, the KPS was identified as predictor of survival in patients irradiated for metastatic bile duct cancer and should be considered when assigning the radiation regimen to an individual patient.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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