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Outcomes After Radio(chemo)therapy for Non-Metastatic Bile Duct Cancer

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Abstract. *Background/Aim: The role of radio(chemo) therapy for non-metastatic bile duct cancer is not well defined. This study provides additional data for this rare situation. Patients and Methods: Data of eight patients receiving radio(chemo)therapy for non-metastatic bile duct cancer were retrospectively analyzed regarding local control, metastases-free survival and overall survival. In addition to the entire cohort, five tumor- or treatment-related factors were investigated: tumor stage, histologic grading, point in time of radio(chemo)therapy, upfront surgery and concurrent chemotherapy. Results: Median overall survival was 37 months. Overall survival rates at 3 and 5 years were 56% and 38%, respectively. Lower histologic grading was significantly associated with better overall survival (p=0.042). Metastases-free survival rates at 3 and 5 years were 38% and 19%, while local control rates were 43% and 21%, respectively. Concurrent radiochemotherapy (vs. radiotherapy alone) resulted in significantly improved local control (p=0.014). Conclusion: Radiochemotherapy can achieve promising results in selected patients with non-metastatic bile duct cancer.*

Bile duct cancers are very rare (1). Although the incidence has constantly increased in Western countries, in the United States during the last forty years it is still below 1/100,000 inhabitants (2, 3). Both local recurrences and distant metastases are quite common. In a retrospective study of 177 patients who underwent potentially curative surgery, 80 patients had bile duct cancer. In the latter group, the median time to progression of disease was 20.3 months and 68% of the patients developed a progression after a median follow-up of 2 years. First site of failure was a local recurrence alone in 59% of these patients and distant metastases with or without a concurrent local recurrence in 41% of patients, respectively (4).

If the intention of treatment is to cure, surgery is considered the treatment of choice. In contrast, radiotherapy with or without concurrent chemotherapy plays only a minor role in the local treatment of non-metastatic bile duct cancers (2). It is considered for selected patients with unresectable tumors or after incomplete resection. Since radiotherapy is seldomly used for treating patients with non-metastatic bile duct cancer, there is a lack of studies. The present study was performed to provide additional data for the role of radiochemotherapy and radiotherapy in the treatment of this rare group of patients.

Patients and Methods

The data of eight patients who received concurrent radiochemotherapy or radiotherapy alone for primary (N=6) or recurrent (N=2) non-metastatic bile duct cancer between 2001 and 2015 were analyzed in this retrospective study regarding local control (freedom from progression of the primary tumor), metastases-free survival (freedom from distant metastases) and overall survival. Histology was adenocarcinoma in seven patients and unknown in one patient. Two patients were female and six male. The median age was 66 years (range, 62-74 years). In addition to the entire cohort, five tumor or treatment related factors were investigated including tumor stage (American Joint Committee on Cancer) at the time of radiotherapy (I *vs.* II *vs.* III *vs.* recurrence), histologic grading (G2 *vs.* G3), point in time of radio(chemo)therapy (primary treatment *vs.* treatment of local recurrence), surgery prior to radio(chemo)therapy (no *vs.* yes) and type of treatment (radiochemotherapy *vs.* radiotherapy alone). The distribution of these factors is summarized in Table I.

Total doses of radiotherapy ranged between 45 Gy and 54 Gy (median dose=50.4 Gy). Doses per fraction were always 1.8 Gy administered on five days per week. Seven patients received concurrent radiochemotherapy, six patients with two courses of 5-fluorouracil (500 mg/m^2/day on five consecutive days every five weeks) and one patient with two courses of cisplatin 25 mg/m^2 and gemcitabine 1,000 mg/m^2 on days 1 and 8 every four weeks.

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Local control, metastases-free survival and overall survival were referenced from the first day of radiotherapy. Analyses were performed with the Kaplan-Meier-method and, if at least two groups were compared, additionally with the log-rank test (5).

Results

Median follow-up times were 21 months (range, 1-61 months) in the entire cohort and 31 months (range, 9-61 months) in patients who were still alive at their last follow-up. The median overall survival time in the entire cohort was 37 months. Overall survival rates at 1, 3 and 5 years were 75%, 56% and 38%, respectively. On survival analysis, lower histologic grading (G2) was significantly associated with a better outcome (p=0.042, Table II).

Distant metastases occurred in five patients (62.5%) after median 23 months (range, 1-50 months). The metastases-free survival rates at 1, 3 and 5 years were 75%, 38% and 19%, respectively. On the analysis of metastases-free survival, none of the investigated tumor and treatment related factors achieved significance (Table III).

A local recurrence was observed in four patients (50%) after median 22.5 months (range, 3-44 months). Local control rates at 1, 3 and 5 years were 86%, 43% and 21%, respectively. On the analysis of local control, concurrent radiochemotherapy, when compared to radiotherapy alone, resulted in a significantly improved outcome (p=0.014, Table IV). Furthermore, a strong trend for better local control was found for lower histologic grading (p=0.059).

Table I. *Tumor- and treatment-related factors.*

	N patients
Tumor stage at radiotherapy	
Stage I	1
Stage II	4
Stage III	1
Recurrence	2
Histologic grading	
G2	3
G3	4
Unknown	1
Point in time of radio(chemo)therapy	
Primary treatment	6
Treatment of local recurrence	2
Surgery prior to radio(chemo)therapy	
No	6
Yes	2
Type of treatment	
Radiochemotherapy	7
Radiotherapy alone	1

Discussion

Since the prognosis of patients with non-metastatic bile duct cancer is generally poor, considerable research is carried out to improve the outcomes of these patients (6-8). Surgery alone is the most commonly administered treatment resulting in 5-year overall survival rates of 15-30% according to registry data and 18-63% according to surgical studies (2). Radiochemotherapy and radiotherapy are generally used only for patients with unresectable or incompletely resected tumors. However, because of a lack of data the true value of radio(chemo)therapy isn't properly clarified yet.

Two retrospective studies suggested that treatment outcomes after microscopically incomplete (R1) resection can be improved with adjuvant radiotherapy. The study of Todoroki *et al*. compared 28 patients with adjuvant radiotherapy to 19 patients without radiotherapy following R1-resection (9). Five-year overall survival rates were 34% and 14%, respectively (p=0.014). In another study, Gwak *et al*. compared 31 patients receiving adjuvant radiotherapy with 40-54 Gy to 47 patients without radiotherapy (10). In the subgroup of patients who received a R1-resection (20 and 27 patients, respectively), median disease-free survival was significantly better in the radiotherapy group (21 *vs*. 10 months, p=0.042).

For initially unresectable tumors, radiochemotherapy was shown to be superior to radiotherapy alone. In the retrospective study of Chen *et al*., both median overall survival (13.5 *vs*. 6.7 months, p=0.003) and median progression-free survival (8.8 *vs*. 4.4 months, p=0.005) were significantly better after radiochemotherapy than after radiotherapy alone (11).

A few other studies were reported that particularly investigated the value of radiochemotherapy for patients with non-metastatic bile duct cancer. In 2007, Hughes *et al*. presented a retrospective study of 34 patients who received a median dose of 50.4 Gy of radiotherapy with concurrent 5-fluorouracil based chemotherapy followed by maintenance chemotherapy (12). Median overall survival was 20 months, which was significantly better than the 8 months of a historic control group of 30 patients (p<0.04). In 2014, Park *et al*. reported the 2-year results of 30 patients treated with radiotherapy (40-55.8 Gy) plus concurrent chemotherapy with 5-fluorouracil or gemcitabine following macroscopically incomplete (R2) resection (13). The 2-year rates of local control, metastases-free survival and overall survival were 33%, 42% and 45%, respectively. Also a prospective series is available. The phase II study of Autorion *et al*. investigated the outcomes of 27 patients with unresectable non-metastatic bile duct cancer who received 50 Gy of radiotherapy plus concurrent gemcitabine-based chemotherapy with or without an additional radiation boost of 15-20 Gy administered with intraluminal high-dose rate brachytherapy (14). The 2-year rates of local control, metastases-free survival and overall survival were 29%, 36% and 27%, respectively.

However, despite these promising results, radiochemotherapy and radiotherapy are uncommon for non-metastatic bile

Table II. *Analysis of overall survival*.

	At 1 year (%)	At 3 years (%)	At 5 years (%)	*p*-Value
Tumor stage at radiotherapy				
Stage I	100	100	n.a.	
Stage II	75	75	75	
Stage III	100	0	0	
Recurrence	50	50	0	0.53
Histologic grading				
G2	100	100	67	
G3	50	0	0	**0.042**
Point in time of radio(chemo)therapy				
Primary treatment	83	56	56	
Treatment of local recurrence	50	50	0	0.33
Surgery prior to radio(chemo)therapy				
No	83	57	n.a.	
Yes	50	50	50	0.98
Type of treatment				
Radiochemotherapy	86	64	43	
Radiotherapy alone	0	0	0	0.13
Entire cohort	75	56	38	

Bold value indicates significant *p*-value.

Table III. *Analysis of metastases-free survival*.

	At 1 year (%)	At 3 years (%)	At 5 years (%)	*p*-Value
Tumor stage at radiotherapy				
Stage I	100	100	0	
Stage II	75	75	75	
Stage III	100	0	0	
Recurrence	50	0	0	0.41
Histologic grading				
G2	100	67	33	
G3	50	0	0	0.16
Point in time of radio(chemo)therapy				
Primary treatment	83	56	28	
Treatment of local recurrence	50	0	0	0.11
Surgery prior to radio(chemo)therapy				
No	83	28	0	
Yes	50	50	50	0.63
Type of treatment				
Radiochemotherapy	86	43	21	
Radiotherapy alone	0	0	0	0.13
Entire cohort	75	38	19	

Table IV. *Analysis of local control*.

	At 1 year (%)	At 3 years (%)	At 5 years (%)	*p*-Value
Tumor stage at radiotherapy				
Stage I	100	100	0	
Stage II	100	100	100	
Stage III	100	0	0	
Recurrence	50	0	0	0.20
Histologic grading				
G2	100	67	33	
G3	67	0	0	0.059
Point in time of radio(chemo)therapy				
Primary treatment	100	67	33	
Treatment of local recurrence	50	0	0	0.15
Surgery prior to radio(chemo)therapy				
No	83	28	0	
Yes	100	100	100	0.17
Type of treatment				
Radiochemotherapy	100	50	25	
Radiotherapy alone	0	0	0	**0.014**
Entire cohort	86	43	21	

Bold value indicates significant *p*-value.

duct cancer, even in case of unresectable or incompletely resected tumors. The present study was performed to provide additional data encouraging the use of radio(chemo)therapy for selected patients. The outcomes were favorable when compared to other studies, particularly in patients receiving radiochemotherapy. Particularly the 5-year overall survival rates of 38% (entire cohort) and 43% (radiochemotherapy group) appeared promising and were well in the range of 18-63% reported for surgical series (2). In the present study, radiochemotherapy resulted in significantly better local control than radiotherapy alone. This finding agrees with the results of the retrospective study of Chen *et al*., where overall survival and progression-free survival were significantly improved in the radiochemotherapy group when compared to the radiotherapy alone group (11). In addition to concurrent chemotherapy, lower histologic grading (G2 *vs*. G3) showed a significantly positive association with outcome in the present study. Lower grading represents a better differentiated and less aggressive tumor.

In conclusion, this study showed promising outcomes particularly after radiochemotherapy when administered to selected patients with non-metastatic bile duct cancer. Thus, radiochemotherapy, either alone or following surgery, should be kept in mind as a potential treatment option for these patients.

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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