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Prolonged chemotherapy impairs liver regeneration after portal vein occlusion – an audit of 26 patients

Short title: Portal vein occlusion

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Abstract

Aim: The aim of the present retrospective study was to investigate the influence of neoadjuvant chemotherapy on liver regeneration after portal vein occlusion before major hepatectomy.

Method: Between 2003 and 2007, 26 patients underwent portal vein occlusion, of whom 22 had portal vein embolisation and 4 portal vein ligation. 15 of 23 patients with colorectal liver metastases had neoadjuvant chemotherapy.

Results: After portal vein occlusion, the ratio of the future liver remnant volume to total parenchymal liver volume (FLR%) was reduced in patients receiving neoadjuvant chemotherapy (27 ± 1 % vs 32 ± 1 %, p=0.03). A smaller future liver remnant before portal vein occlusion resulted in a greater degree of hypertrophy ($r^2=0.18$, $p=0.04$). Patients with tumour size greater than 60 mm showed a decreased degree of hypertrophy (7 ± 1) % as compared to patients with smaller tumours (13 ± 1 %, $p=0.01$). There was one death shortly after portal vein embolisation. 19/26 patients were resected with zero operative mortality.

Conclusion: Prolonged neoadjuvant chemotherapy has a small negative effect on liver regeneration induced by portal vein occlusion. Liver regeneration induced by portal vein occlusion is relatively large when tumour burden is small.

Key words portal vein embolisation, liver, chemotherapy, regeneration
Introduction

Surgical resection is used with increasing frequency for hepatobiliary malignancies in order to provide a chance for cure. One major limitation to the extent of resection is the remnant liver volume. In patients with normal liver parenchyma, a remnant volume of >25% of initial liver volume is considered sufficient to allow resection with an acceptably low risk of post-operative liver failure [1].

When the future liver remnant, FLR, is considered too small, portal vein occlusion (PVO) can be used. Portal vein occlusion, which includes embolisation and ligation, is performed to increase the volume of the future liver remnant before major hepatectomy. After occlusion, the liver is allowed to regenerate during approximately three-four weeks, followed by resection [2, 3].

For colorectal liver metastases, there is growing evidence showing that neoadjuvant chemotherapy before hepatectomy prolongs survival [4, 5]. Preoperative chemotherapy can be used to downsize tumors to become resectable [6]. In the following, chemotherapy administered before hepatectomy will be referred to as neoadjuvant chemotherapy.

Extensive neoadjuvant chemotherapy for colorectal cancer may induce hepatic damage [7] and increase morbidity [8] and even short-term mortality [9] after hepatectomy. The lower limit of liver remnant volume to ensure safe resection after chemotherapy has not been established, but a minimal liver remnant of 30-40% has been proposed [10]. If preoperative portal vein occlusion is required, neoadjuvant chemotherapy is also frequently used to minimize the risk of tumour progression during the time interval between occlusion and resection. Previous clinical studies have shown no or only modest impact by neoadjuvant chemotherapy on liver regeneration after portal vein occlusion [3, 11, 12]. On the other hand,
adjuvant chemotherapy has been shown to cause suppression and delay of regeneration after partial hepatectomy in rats [13].

The aim of the present retrospective study was to evaluate the significance of preoperative chemotherapy and tumour size on regenerated volume after portal vein occlusion.
Methods

Patients

Between June 2003 and July 2007, the records of 26 consecutive patients who underwent portal vein occlusion in preparation for extended right hepatectomy, i.e., a planned resection of Couinaud’s segments 4-8, with or without resection of the caudate lobe (segment 1), were reviewed. Portal vein occlusion was considered to be indicated when the future liver remnant volume to total parenchymal liver volume (FLR%) was <20% in patients without chemotherapy and <30%, preferably <35%, in patients with chemotherapy.

Patient characteristics are shown in Table 1. No patient had any known liver parenchymal disease and all had normal values of bilirubin and international normalized ratio (INR) prior to intervention. Indications for neoadjuvant chemotherapy in patients with colorectal liver metastases were multiple (>5) liver tumours in 13 patients and downsizing in 2.

Volumetric assessment

Liver volumetry was made in 19 cases by the MeVis institute (Bremen, Germany) using computed tomography images with 1 mm slices, giving the volume of the left lateral segment, total liver volume and tumour volume. In seven patients volumetry was manually assessed at our institution using computed tomography or magnetic resonance images. The contours of the left lateral segment, the whole liver and liver tumours were traced manually on each 5 mm slice, the areas were automatically calculated and volumes were obtained by summation of areas and multiplying by the distance between slices. Liver parenchymal volume was calculated by subtracting tumour volume from total liver volume. The future liver remnant percentage, FLR%, was calculated as the quotient between the volume of future liver
remnant and liver parenchymal volume. Initial evaluation was made using the first volume measurements after portal vein occlusion. Final evaluation employed the last measurements before the decision to resect or not. The degree of hypertrophy, DH, was defined as the difference in FLR% before portal vein occlusion and after initial or final evaluation.

*Portal vein embolisation*

Right portal vein embolisation was performed on 22 patients, including 3 patients who, in addition, received embolisation to the medial segment (segment 4). Patients received a single dose of intravenous antibiotic prophylaxis before the procedure. In general or local anaesthesia with iv sedation, percutaneous access to the portal system was gained under sonographic and/or fluoroscopic guidance with a 20 G needle. The approach was ipsilateral in 20 patients, and contralateral in 2, including one where puncture from the right side failed. Using the Seldinger technique, a 5 Fr introducer system was inserted after portography with a 5 Fr Omniflush catheter (Cordis, Johnson & Johnson) in the main trunk of the portal vein to delineate the portal system. Selective catheterization of the target segmental branches of the portal vein was made using Sidewinder or Cobra catheters (Cordis, Johnson & Johnson). Polyvinyl particles 250-750 µm in size (Contour, Boston Scientific) were used for embolisation until cessation of flow. After occlusion of all segmental branches, a final venogram was obtained with the flush catheter in the main portal vein to evaluate the completeness of embolisation. If needed, additional embolisation was performed until satisfactory results were achieved. At the end of the procedure, the percutaneous tract was embolised with gelatine sponge (Spongostan-Standard, Cook Europe). After portal vein embolisation, repeat volumetry based on computed tomography was scheduled after approximately 3 weeks. If recanalisation of segmental portal branches to the right liver was
found, and the liver regeneration was judged insufficient, a second portal embolisation was attempted.

*Portal vein ligation*

Right portal vein ligation was performed in 4 patients, 2 of whom had neoadjuvant chemotherapy. These patients were scheduled for right hepatectomy (segments 5-8) but had unexpected intraoperative findings of tumour extension necessitating an extended right hepatectomy (segments 4-8 ±1) for tumour clearance. Ligation was performed by dissecting the right portal branch at the hilum and dividing it with a vascular stapler. During the study time period an additional four patients underwent portal vein ligation as part of a two-stage operation. As these procedures included resection of a substantial portion of the left lateral segment (segments 2-3), these patients were excluded from the present analysis.

*Tumour size and response*

In patients with colorectal liver metastases, tumour response evaluation was based on liver imaging before and after PVO according to Response Evaluation Criteria in Solid Tumors (RECIST) [14].

*Chemotherapy*

Chemotherapy was administered to 15 of 23 patients, all with colorectal liver metastases, prior to portal vein occlusion. The regimens, the type of which was decided by the referring oncologist, included oxaliplatin in combination with 5-fluorouracil (FOLFOX) in 8 patients. One patient received irinotecan in combination with 5-FU (FOLFIRI), one patient was treated with FOLFOX in combination with bevacuzimab and one patient had FOLFIRI in combination with cetuximab. Some patients was given two lines of chemotherapy, including
FOLFOX followed by FOLFIRI (2 patients), FOLFOX followed by FOLFIRI+cetuximab (1 patient) and capecitabine in combination with oxaliplatin followed by FOLFOX (1 patient).

Patients received 9 (4-29) (median, range) cycles of neoadjuvant chemotherapy during 23 (8-83) weeks before portal vein occlusion. Chemotherapy was stopped 3 (1-11) weeks before the first portal vein occlusion. It was restarted after 2 (0-8) weeks, and 1.5 (0-5) cycles were given during 2.5 (0-13) weeks before CT-based decision of surgery or palliative treatment, or 2 (1-3) weeks before the second portal vein occlusion. The interval between the second portal vein occlusion and chemotherapy was 2 (1-4) weeks and a further 3 (2-7) cycles were given during 4 (1-15) weeks before final CT. Chemotherapy was administered in the time interval between portal vein occlusion and final volume evaluation in all of the 15 patients receiving neoadjuvant chemotherapy in addition to one patient without prior chemotherapy in order to halt tumour progression after PVO.

Liver resection

Hepatectomy was performed using standard technique. In brief, the liver was mobilized through a bilateral subcostal incision with upwards midline extension. Intraoperative ultrasound was used in all patients. The right portal vein and right hepatic artery were divided extrahepatically. Parenchymal transection was made using an ultrasound aspiration dissector (CUSA®, Valleylab Inc, Boulder, CO) with selective use of Pringle’s manoeuvre.

Complications

In-hospital postoperative complications were recorded. Hepatic failure was defined as a bilirubin value > 50 µmol/l or an INR >1.7 at postoperative day 5 [15].
Statistical analysis

Data are expressed as means ±SEM unless stated otherwise. Mann-Whitney U-test or Wilcoxon test was used to compare continuous data between groups. Fisher’s exact test was used for 2x2 categorical data. All tests were two-sided. A p value less than 0.05 was considered statistically significant.
Results

Procedures

Portal vein embolisation was technically successful in 22 of 23 patients. In one patient two attempts failed to provide access to the portal system, and portal vein ligation was subsequently performed. There was one death occurring the day after embolisation. The patient, a 66 year-old male, had received extensive neoadjuvant chemotherapy for downstaging of liver metastases of colorectal origin prior to embolisation. Autopsy revealed circulatory collapse as cause of death, with no evidence of direct treatment-related causes. No other complications were noted and the median hospital stay after the procedure was 1 day, (range 1-4 days).

Portal vein ligation was performed on 4 patients, including the one patient in whom the embolisation failed. No complications occurred. The median hospital stay was 7 days (range 6-13 days).

Efficacy

The effect on liver volume after PVO was first evaluated after a median time of 22 days after occlusion (range 6-34 days). Ten patients with inadequate hypertrophy (see below) showed radiological signs of patent segmental branches of the right portal vein, which were judged accessible to repeat portal vein embolisation. These patients were subjected to a second right portal vein embolisation. Two patients with inadequate regeneration and an obliterated right portal venous system underwent a second portal vein embolisation to segment 4. Thus, 12 of 25 patients were embolised twice. Three of 11 patients without chemotherapy received 2 embolisations as compared to 9 of 14 patients with neoadjuvant chemotherapy. In the group of patients who underwent ligation or were embolised once, open
segmental branches were occasionally seen, but as regeneration was considered sufficient to allow a safe resection, no further embolisation attempts were made.

Influence of chemotherapy

Before PVO, there was no significant difference in FLR% between groups with and without chemotherapy (18 ± 1 % and 20 ± 1 %, respectively; p=0.11). After PVO, FLR% was lower in patients with (27 ± 1 %) than in patients without chemotherapy (32 ± 2 %) (p=0.03, Fig. 1). Adequate hypertrophy, as judged by radiological evaluation, was obtained after 59 (median; range 6-157) days in the chemotherapy group, and after 30 (median; range 12-119) days in the group without chemotherapy. The future liver remnant volume increased from 268 ± 22 cm$^3$ to 393 ± 24 cm$^3$ in patients with chemotherapy, and from 337 ± 23 cm$^3$ to 490 ± 35 cm$^3$ in patients without chemotherapy.

Influence of tumour size and future liver remnant volume before occlusion

There was a negative correlation between FLR% before portal vein occlusion and the degree of hypertrophy, i.e., the degree of hypertrophy was larger the smaller the FLR% before portal vein occlusion ($r^2=0.18$, p=0.04; Fig. 2).

FLR% before portal vein occlusion was related to tumour size ($r^2=0.22$, p=0.02; Fig. 3), i.e., the larger the tumour the larger the FLR% before portal vein occlusion. For instance, patients with tumours larger than 60 mm had a larger FLR% before PVO than patients with tumours less than 60 mm (21 ± 1 % vs 17 ± 1 %; p=0.03). As compared to patients with tumours larger than 60 mm, patients with tumours less than 60 mm had a greater degree of hypertrophy (13 ± 1 % vs 7 ± 1 %; p=0.01; Fig. 4).
In patients with colorectal cancer metastases tumour size did not differ between patients with and without chemotherapy, neither before nor after portal vein occlusion (p>0.05 in both situations).

Rate of resection

The total number of resected patients was 19 out of 26. Four patients were excluded without surgical exploration due to death after portal vein embolisation (n=1), bad general condition (n=1), and inadequate growth of future liver remnant (n=2). Three patients were excluded at exploration because of unexpected peritoneal carcinomatosis (n=1) and unanticipated massive tumour extension in the liver precluding resection (n=2). Of these 7 patients, 4 had had neoadjuvant chemotherapy and 3 had not.

Operative outcome

Seventeen patients underwent extended right hepatectomy (segments 4-8) with or without resection of segment 1, together with an atypical resection in the left lateral segment in four patients. Another two patients had a right hepatectomy (segments 5-8), because of intraoperative findings of a more limited liver tumour distribution than expected. Pathological examination revealed 15 cases of R0 resection (resection line free of tumour), and 4 cases of R1 resection. After resection, there were no deaths within 30 days of surgery. In-hospital complications are shown in Table 2. Median hospital stay was 10 days (range 7-28 days) in the neoadjuvant chemotherapy group and 11 days (range 8-18 days) in the group without chemotherapy, respectively.
Discussion

*Suppressed liver regeneration after chemotherapy*

In the present study neoadjuvant chemotherapy led to less hypertrophy of the future liver remnant. This contrasts with previous studies that have failed to show an effect on liver regeneration by concomitant chemotherapy for colorectal liver metastases [3,16, 17], although the extent of treatment was not accounted for in the latter 2 studies. In addition, chemotherapy between embolisation and surgery has been suggested not to influence the regenerating capacity of the liver [11,18]. It is possible that the prolonged chemotherapy used in the present study, where the number of chemotherapy cycles pre PVO was, for instance, double the number the cycles reported in the study by Ribero et al [3], explains the difference in outcome.

*Rationale for portal vein occlusion*

It has been shown that a FLR% less than 20% and/or a degree of hypertrophy less than 5% is associated with an increased morbidity [3]. In the present study, no resected patient had a FLR% less than 20% after portal vein occlusion.

Both embolisation and ligation was used for portal vein occlusion in the present study. Results from previous clinical investigations indicate that the two methods are equal in inducing hypertrophy of the future liver remnant [19,20], although one study has shown ligation to be inferior to embolisation [21].
**Influence of tumour size on regeneration**

In livers with normal parenchyma and without tumours, the left lateral segment constitutes less than 20% of total liver volume in 75% of patients [22]. Therefore, in absence of compensatory hypertrophy by tumour growth, preoperative portal vein occlusion is indicated in many patients planned for an extended right hepatectomy (segments 4-8 ± 1). We found that large tumours before occlusion resulted in less hypertrophy of the future liver remnant. Since the FLR% before occlusion was larger for patients with large tumours, one explanation could be that the process of hypertrophy had already begun in patients with larger tumours. This process could be analogous to the reduced liver regeneration after hepatectomy in patients who have undergone preoperative portal vein embolisation [23]. The negative correlation between FLR% before PVO and degree of hypertrophy, as shown in Fig. 2, has been described previously [24], but we are unaware of previous results connecting tumour size to the degree of hypertrophy (Figs. 3-4). One previous study on mostly hepatocellular carcinomas failed to shown any association between hypertrophy and tumour size [25].

**Morbidity and mortality**

Death after portal vein embolisation has not been previously reported. The diseased patient had been treated with chemotherapy (FOLFOX, followed by FOLFIRI and FOLFIRI + cetuximab) for 29 months (51 cycles) due to colorectal metastases confined to the liver. Eventually, this resulted in downstaging of the disease and portal vein embolisation was performed. Post-mortem examination could not reveal any cause of death directly related to the embolisation procedure. No other complications were noted after embolisation. Portal vein embolisation is generally considered safe with a morbidity rate of approximately 10%, mainly consisting of transient abdominal pain and fever [2].
Chemotherapy induces hepatic injury [7] and some [8,9] but not all [26] studies suggest that this augments the morbidity and short-term mortality after hepectomy. The effect of combining preoperative chemotherapy and portal vein occlusion on morbidity after hepectomy has not yet been specifically addressed. It appears that the addition of chemotherapy to portal vein occlusion did not increase the rate of complications after hepectomy (Table 2).

Repeat portal vein embolisation

In comparison to previously reported results, we had a high proportion of patients which we considered would gain from repeated portal vein embolisation. Twelve of 25 patients were embolised twice. The decision was based on inadequate hypertrophy coupled with radiological signs of patent segmental branches, as displayed on follow-up computed tomography. These branches were considered recanalised as the portograms obtained at the end of the first embolisation in all cases revealed complete stasis of right portal branches. After the repeat procedure, the hypertrophy was equal to what was seen in patients embolised once. Our standard technique was right portal embolisation since this has been shown to give a similar volume increase of the left lateral segment as right portal vein embolisation with inclusion of segment 4 branches [27]. We used polyvinyl particles only, which has been reported to provide efficient and durable portal vein occlusion [28], although other investigators add microcoils deployed in segmental portal branches [29]. Recent experimental results indicate that reversible portal vein occlusion also induces liver hypertrophy [30], but the present results indicate that the goal should be complete and permanent occlusion of the target portal branches to maximize regeneration.
Conclusions

In conclusion, the present study has shown that prolonged neoadjuvant chemotherapy decreases liver regeneration after portal vein occlusion. Liver regeneration after portal vein occlusion is relatively large when the FLR% before embolisation is small and when liver tumour burden is small.
References


**Table 2** Morbidity after hepatectomy

<table>
<thead>
<tr>
<th>Complication</th>
<th>Neoadjuvant chemo-therapy (n=11)</th>
<th>No chemo-therapy (n=8)</th>
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</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Drainage of ascites</td>
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<td>2</td>
</tr>
<tr>
<td>Pleural fluid requiring drainage</td>
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<td>1</td>
</tr>
<tr>
<td>Biliary fistula</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
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<td></td>
</tr>
<tr>
<td>Patients with complications</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>
Figure legends

**Fig. 1** Change in mean (SEM) relative volumes of future liver remnant to total parenchymal liver volume (FLR%). PVO = portal vein occlusion

**Fig. 2** Linear regression of the resulting degree of hypertrophy after portal vein occlusion (PVO) and relative volume of future liver remnant to total parenchymal liver volume before PVO (FLR%), P=0.035

**Fig. 3** Linear regression of the relative volume of future liver remnant to total parenchymal liver volume before portal vein occlusion (FLR%) and tumor size before occlusion (P=0.017)

**Fig. 4** The degree of hypertrophy for different tumor sizes. Tumor size was measured before portal vein occlusion.