Major Liver Resection for Carcinoma in Jaundiced Patients Without Preoperative Biliary Drainage

Daniel Cherqui, MD; Stéphane Benoist, MD; Benoît Malassagne, MD; Roberto Humeres, MD; Virginia Rodriguez, MD; Pierre-Louis Fagniez, MD

Background: The role of preoperative biliary drainage (PBD) before liver resection in the presence of obstructive jaundice remains controversial. Our patients with proximal duct carcinoma undergo noninvasive assessment followed by rapid laparotomy without PBD if the lesion is deemed resectable.

Hypothesis: Our aim was to report operative outcome of these patients and to analyze their specific features by comparison with patients without biliary obstruction who underwent major liver resection.

Design: A case-comparison study.

Setting: A tertiary care university hospital in a metropolitan area.

Patients: Twenty consecutive jaundiced patients underwent major liver resection without PBD. The jaundiced patients were matched with 27 nonjaundiced patients with normal underlying liver selected from a computer bank of 261 patients undergoing liver resections and identical for age, tumor size, type of liver resection, and vascular occlusion.

Main Outcome Measure: Postoperative course including mortality, morbidity, transfusion rates, and results of liver function tests.

Results: Seventeen jaundiced patients (85%) and 13 nonjaundiced patients (48%) received blood transfusions ($P = .03$). Morbidity was 50% in jaundiced and 13% in nonjaundiced patients ($P = .006$), mainly resulting from subphrenic collections and bile leaks occurring only in jaundiced patients. In contrast, there were no significant differences for mortality (5% vs 0%) and liver failure (5% vs 0%). Postoperative changes in liver function test results were comparable between groups.

Conclusions: Major liver resections without PBD are safe in most patients with obstructive jaundice. Recovery of hepatic synthetic function is identical to that of nonjaundiced patients. Transfusion requirements and incidence of postoperative complications, especially bile leaks and subphrenic collections, are higher in jaundiced patients. Whether PBD could improve these results remains to be determined.

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Liver resections in jaundiced patients are associated with significant rates of mortality and morbidity, resulting mainly from the development of postoperative complications such as sepsis, bleeding, and liver failure. Because retrospective reports suggested a direct relationship between serum bilirubin concentration and the risks of operation, routine preoperative biliary drainage (PBD) has been advocated before definitive surgery with the aim of reducing morbidity and mortality.

Four prospective randomized trials failed to demonstrate a specific benefit of PBD and associated PBD with specific complications that could overcome any apparent benefit. However, these controlled trials included patients with various benign and malignant diseases and with very few liver resections. Because liver resections in jaundiced patients were considered to carry a special risk, many authors continued to recommend PBD in this setting. In the absence of demonstrated benefits of PBD, our policy has been to use noninvasive assessment followed by immediate operation, without PBD, in patients undergoing liver resection for high malignant obstructive stricture.

Our aim was to analyze the postoperative course of jaundiced patients who underwent major liver resections without PBD and to compare these results with those obtained in a control group of matched patients without biliary obstruction.

RESULTS

PATIENT CHARACTERISTICS

The indications for liver resections in the jaundiced and control groups are listed in Table 1. The main indication was cho-
PATIENTS AND METHODS

PATIENTS

From January 1, 1991, through December 31, 1998, 20 patients with obstructive jaundice due to proximal bile duct carcinoma underwent liver resection without PBD. Jaundice was defined as a serum total bilirubin level higher than 100 µmol/L (5.8 mg/dL). Proximal bile duct carcinoma included hilar cholangiocarcinoma (Klatskin tumor), gallbladder cancers extending to the biliary confluence, and intrahepatic cancers invading the hepatic hilus. In addition, 2 patients with intrahepatic carcinoma had obstructive jaundice caused by tumor debris obstructing the common bile duct. There were 10 men and 10 women with a mean age of 60 years (range, 40-80 years). During the same period, 4 patients had PBD before resection. Three underwent drainage before referral, and we elected drainage in another because of obstructive jaundice of more than 1 month. These patients were excluded from the study.

Preoperative assessment included complete physical examination, Doppler ultrasound, and helical computed tomographic (CT) scan of the abdomen. Magnetic resonance cholangiography was performed for the last 9 patients (Figure 1). No patient underwent preoperative percutaneous or retrograde cholangiography. The noninvasive assessment was followed by early laparotomy within 1 week of admission. The liver was approached through a bilateral subcostal incision with upper midline extension. Surgical exploration included intraoperative ultrasonography and hilar and porta hepatitis dissection. Transcystic cholangiography was performed when feasible (Figure 2). Macroscopic evaluation was associated with frozen-section studies as soon as suspicious tissue was encountered.

The decision was based on these findings, which determined the side and the extent of liver resection. The liver was mobilized, and the inferior vena cava was exposed. Extrahepatic division of the hepatic artery and the portal vein was performed before resection. Vascular clamping of the remnant liver were avoided whenever possible, and in the last 2 years intermittent clamping was used. In Klatskin tumors, resection of caudate lobe was performed systematically. Liver transection was performed using Kelly forceps, and vascular and biliary structures were secured by sutures and clips. Biliary procedures included resection of the biliary confluence and Roux-en-Y intrahepatic hepaticojejunostomy in 18 patients and common bile duct exploration with T-tube drainage for removal tumor debris in 2. Lymphadenectomy of the porta hepatitis was performed in all patients. Systematic samples of intrahepatic bile were collected for culture. Fibrin glue was applied to the liver resection margin, and a subphrenic closed-suction drain was placed.

CONTROL GROUP

As previously described, patients with obstructive jaundice were compared with matched controls without jaundice. During the study period, 261 liver resections were performed for various hepatic diseases with a 6.5% hospital mortality rate. Patients without jaundice were selected from the computer bank to constitute a control group. During the selection process, the investigators were unaware of operative morbidity and mortality. For each patient with malignant obstructive jaundice, subjects with underlying normal liver were selected, matching the following criteria: age, tumor size, number of tumors, type of liver resection, and type and duration of vascular occlusion. Twenty-seven patients fulfilled all selection criteria and formed the control group.

STUDIED CRITERIA

The patients underwent analysis until the day of discharge. Complications were considered if discharge was delayed or further intervention was required. In the presence of fever, ultrasound or CT scan was performed. When a subphrenic collection was present, needle aspiration was performed for culture, and bilirubin concentration was measured in the fluid. Biliary fistula was defined as bilirubin-rich fluid (bilirubin concentration of >3 times serum concentration) collected from needle aspiration or abdominal drainage. Bilomas and infected subphrenic collections were drained percutaneously under CT guidance. Liver tolerance to ischemia was assessed by postoperative serum aminotransferase activity. Liver failure was defined as a fall of prothrombin activity below 30% and signs of hepatic encephalopathy. Mortality was defined as death occurring in the hospital or within 30 days. The results are expressed as mean ± 1 SD. Comparisons between groups were analyzed using the chi² test with Yates correction, or the Mann-Whitney test for qualitative and quantitative variables as appropriate. Significance was defined as P<.05.

Surgical Procedures

Except for associated biliary procedures, the surgical interventions were similar in both groups (Table 3). Clamping methods were also equally distributed. The mean duration of surgery was 360 ± 78 minutes (range, 240-510 minutes) in the jaundiced group vs 240 ± 71 minutes (range, 180-420 minutes) in the control group (P<.001). In the jaundiced group, bile was sterile at the time of surgery in all cases.

BLOOD TRANSFUSIONS

Perioperative transfusions (ie, intraoperative and postoperative) were analyzed. Seventeen jaundiced patients (85%) and 13 nonjaundiced patients (48%) received blood transfusions (P = .03). However, only 1 jaundiced patient required 10 U packed red blood cells. The mean number of units transfused was 5.2 ± 2.7 (range, 2-10) in the jaundiced group vs 3.2 ± 1.1 (range, 1-5) in the control group (P<.001).
MORTALITY AND MORBIDITY

In the jaundiced group, 1 patient (5%) died 90 days after extended right hepatectomy with bile duct reconstruction for Klatskin cholangiocarcinoma. This patient recovered from severe postoperative liver failure, but secondary acute pancreatitis developed, leading to multiple organ failure and death. As listed in Table 4, 10 patients (50%) in the jaundiced group and 4 (15%) in the control group experienced postoperative complications (P = .006). Subphrenic collections (P = .02) and bile leaks (P = .04) were more frequently observed in the jaundiced group than in control group. Two biliary fistulas were treated by maintenance of abdominal drainage placed at surgery. A third biliary fistula presented as a biloma and sealed after percutaneous drainage. Three other subphrenic collections were infected and successfully treated by CT-guided percutaneous drainage.

The mean duration of the postoperative hospital stay was 28 ± 14 days (range, 6-90 days) in the jaundiced group vs 15 ± 9 days (range, 7-38 days) in the control group (P < .001).

LABORATORY TESTS

The postoperative changes in liver function tests are shown in Figures 3, 4, and 5. Prothrombin activity fell in both groups at day 1 but was followed by a 45% increase at day 7 (Figure 3). After a similar rise of serum aminotransferases level in both groups at day 1, these returned to preoperative values at day 5 (Figure 4). The concentration of γ-glutamyltransferase and alkaline phosphatase decreased until day 5 in the jaundiced group. Thereafter, the variations of these enzymes were not significantly different between groups (Figure 5).

COMMENT

To identify specific complications observed in jaundiced patients undergoing major liver resection, we undertook this study reporting morbidity and mortality after liver resection in patients with undrained jaundice and comparing these results with those of controls without biliary obstruction. Our study showed that there were no differences in liver failure and mortality rates after liver resection in either group. However, transfusion requirements and morbidity rate were significantly higher in patients with obstructive jaundice. Significant differences in postoperative complications included bile leaks and subphrenic abscesses, which occurred more frequently...
Because we do not use PBD, we attempt to schedule surgery in patients with obstructive jaundice due to proximal bile duct cancer as soon as possible. Our policy is to perform a simple and noninvasive preoperative imaging workup before rapid laparotomy. The purpose of preoperative assessment is to identify patients unsuitable for surgical exploration. Contraindications to surgery include involvement of the main trunk of the portal vein or hepatic artery, distant metastasis, or distal bilateral biliary duct extension. More recently, we have used magnetic resonance cholangiography, which accurately predicts the level of neoplastic biliary duct obstruction. Finally, tumor resectability is best assessed by surgical exploration.

in jaundiced patients and accounted for increased hospital stay.

Because we do not use PBD, we attempt to schedule surgery in patients with obstructive jaundice due to proximal bile duct cancer as soon as possible. Our policy is to perform a simple and noninvasive preoperative imaging workup before rapid laparotomy. The purpose of preoperative assessment is to identify patients unsuitable for surgical exploration. Contraindications to surgery include involvement of the main trunk of the portal vein or hepatic artery, distant metastasis, or distal bilateral biliary duct extension. More recently, we have used magnetic resonance cholangiography, which accurately predicts the level of neoplastic biliary duct obstruction. Finally, tumor resectability is best assessed by surgical exploration.

In our study, the overall morbidity rate of 50% after liver resection in jaundiced patients was significantly higher than the 15% rate observed in controls. Bile leaks and subphrenic collections occurred more frequently in jaundiced patients. This is probably secondary to dilatation of intrahepatic bile ducts and opening of the intestinal tract. Bile was sterile at the time of surgery in all of our patients. The incidence of bile leaks and subphrenic collections compare with those reported in patients having undergone PBD in whom bile infection secondary to PBD

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**Table 3. Types of Operative Procedures**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Jaundiced Group (n = 20)</th>
<th>Control Group (n = 27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major liver resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right or extended right hepatectomy</td>
<td>12 (60)</td>
<td>15 (56)</td>
<td>NS</td>
</tr>
<tr>
<td>Left or extended left hepatectomy</td>
<td>7 (35)</td>
<td>11 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Central hepatectomy</td>
<td>1 (5)</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of resected segments, mean ± SD</td>
<td>4.6 ± 0.8</td>
<td>4.2 ± 1</td>
<td></td>
</tr>
<tr>
<td>Associated procedure</td>
<td>20 (100)</td>
<td>6 (22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bile duct reconstruction</td>
<td>18 (90)</td>
<td>2 (7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Common bile duct exploration</td>
<td>2 (10)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Colonic resection</td>
<td>0</td>
<td>2 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Partial diaphragmatic resection</td>
<td>0</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>0</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Vascular clamping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total vascular exclusion</td>
<td>5 (25)</td>
<td>6 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>Portal triad clamping</td>
<td>7 (35)</td>
<td>11 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemia duration, mean ± SD, min</td>
<td>32.2 ± 16</td>
<td>30 ± 12.8</td>
<td>NS</td>
</tr>
<tr>
<td>No clamping of the remnant liver</td>
<td>8 (40)</td>
<td>10 (37)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as number (percentage) of patients. NS indicates not significant.

**Table 4. Postoperative Complications**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Jaundiced Group (n = 20)</th>
<th>Control Group (n = 27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subphrenic collection</td>
<td>4 (20)</td>
<td>0</td>
<td>.02</td>
</tr>
<tr>
<td>Biliary fistula</td>
<td>3 (15)</td>
<td>0</td>
<td>.04</td>
</tr>
<tr>
<td>Multiple organ failure</td>
<td>1 (5)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>2 (10)</td>
<td>3 (11)</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1 (5)</td>
<td>2 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Chest infection</td>
<td>1 (5)</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>1 (5)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Transient ascites</td>
<td>3 (15)</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Liver failure</td>
<td>1 (5)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with complications</td>
<td>10 (50)</td>
<td>4 (15)</td>
<td>.006</td>
</tr>
</tbody>
</table>

*Some patients had more than 1 complication. Data are given as number (percentage) of patients. NS indicates not significant.
might represent an additional risk factor. Bile leaks and subphrenic collections were treated by nonoperative measures such as percutaneous drainage or maintenance of abdominal drain. Previous studies indicated that abdominal drainage could be omitted after liver resection, and this is our policy in most instances. However, because of the higher incidence of bile leaks and subphrenic collection in jaundiced patients, we recommend routine abdominal drainage in these patients.

The main issue is to evaluate whether the rate of specific complications observed in our jaundiced patients could be reduced by PBD. Ideally, this should be addressed by a prospective randomized trial, which is difficult to perform because proximal bile duct carcinoma is rare and associated with a low resectability rate. This is reflected by the limited number of patients undergoing resection in each individual series during long studies. However, retrospective data and case series may yield interesting information. In a study comparing patients undergoing and not undergoing drainage, there were significantly higher rates of bacterobilia and infectious complications in the group undergoing drainage, and operative time and blood loss were similar. Case series from expert groups, with and without PBD, report identical mortality, morbidity, and blood loss, which are comparable to our data (Table 5).

Objectives of PBD before liver resection include improvement of surgical conditions by increasing the tolerance of cholestatic liver to ischemia and decreasing the blood loss, and reduction of mortality and morbidity. In our study, there were no significant differences between jaundiced patients and controls for tolerance to hepatic ischemia as assessed by the postoperative rise of aminotransferase levels, despite higher preoperative activity in jaundiced patients. By contrast, the transfusion rate and the mean duration of surgery were significantly higher in jaundiced patients. Possible hemostatic alterations may be associated with jaundice, but no reoperation for bleeding was necessary in our series. Furthermore, comparable blood losses and transfusion rates are reported in patients subjected to PBD. We believe that increased bleeding results mainly from the complexity of surgical procedures required for resection of hilar lesions (hilus dissection and associated biliary reconstructions) rather than hyperbilirubinemia. In addition, most bleeding during liver resections reportedly occurs before and after liver transection when appropriate clamping methods are used.

Additional aims of PBD include improvement of postoperative liver function and regeneration capacity that presumably are impaired. Therefore, PBD theoretically should reduce the risk for postoperative liver failure and death. However, in our study, the rate of liver failure in jaundiced patients was low (5%), and recovery of liver synthetic function, assessed by prothrombin activity, was identical to that of controls. Clinical and experimental data suggest that postoperative increase of alkaline phosphatase and γ-glutamyltransferase levels reflect liver regen-

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**Table 5. Results of Liver Resection for Obstructive Jaundice**

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Period of Inclusion, y</th>
<th>No. of Patients‡</th>
<th>Operative Mortality, %</th>
<th>Operative Morbidity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>8</td>
<td>20</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>Without PBD</td>
<td>30</td>
<td>23</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Bismuth et al,17</td>
<td>1992</td>
<td>30</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Childs and Hart,16</td>
<td>1993</td>
<td>10</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>Parc et al,18 1997</td>
<td></td>
<td>12</td>
<td>33</td>
<td>15.2</td>
</tr>
<tr>
<td>Pichlmayr et al,24</td>
<td>1995</td>
<td>18</td>
<td>43</td>
<td>9.3</td>
</tr>
<tr>
<td>Pichlmayr et al,25</td>
<td>1996</td>
<td>13</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>Makuuchi et al,36</td>
<td>1990</td>
<td>7</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Nimura et al,11</td>
<td>1991</td>
<td>14</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>Ogura et al,34</td>
<td>1993</td>
<td>15</td>
<td>33</td>
<td>3.6</td>
</tr>
<tr>
<td>Miyagawa et al,12</td>
<td>1995</td>
<td>5</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Washburn et al,13</td>
<td>1995</td>
<td>9</td>
<td>26</td>
<td>7.6</td>
</tr>
<tr>
<td>Nakajima et al,29</td>
<td>1996</td>
<td>22</td>
<td>109</td>
<td>3.6</td>
</tr>
<tr>
<td>Su et al,4 1996</td>
<td>12</td>
<td>33</td>
<td>15.2</td>
<td>51.5</td>
</tr>
</tbody>
</table>

* PBD indicates preoperative biliary drainage.
† Listed chronologically.
‡ Indicates only patients undergoing resection.
§ Includes patients undergoing and not undergoing drainage.
eration.13,44 In our study, activity of these enzymes in the jaundiced group showed an initial sharp decrease due to biliary decompression but secondarily a reincrease, as in controls. This may be another indicator of liver regeneration in these patients. One patient died of multiple organ failure secondary to acute pancreatitis. This 5% mortality rate was also comparable to that reported after liver resection following PBD.28,34,36 As other authors,30,35,45 we believe that multifactorial causes, including age, nutritional status, bile infection, hypoalbuminemia, and other co-morbidity factors, contribute to a higher mortality rate. Preoperative albuminemia was significantly lower in our jaundiced patients than in controls. This probably reflects the negative impact of biliary obstruction on nutritional status. However, mean albuminemia in jaundiced patients was only moderately reduced (35 vs 40 g/L), which reflects early evaluation, postoperative albuminemia by PBD, which has an effect on hyper-bilirubinemia only.5,10 For these reasons, we advocate early rather than delayed treatment in these patients.

In contrast to its theoretical advantages, PBD is associated with specific complications including bile peritonitis, cholangitis, and bleeding.6,10,16,47 In addition, tumor seeding along catheter tracts has been reported after percutaneous biliary drainage47 and could compromise the results of curative resection. For these reasons, we and others17,18,23 consider that PBD should not be used as a routine procedure before liver resection for obstructive jaundice.

Although we do not recommend routine use of PBD in all patients with malignant obstructive jaundice, we, like others,17,19,29 believe that it is indicated in selected patients such as severely malnourished or hypoalbuminemic patients or those suffering from acute cholangitis or long-standing jaundice. If PBD is used, it should drain the future remnant liver. Furthermore, when preoperative portal embolization is indicated to induce hypertrophy of the future remnant liver, biliary drainage is mandatory.36,38

CONCLUSIONS

Our results suggest that major liver resections without PBD are safe in most patients with obstructive jaundice. However, transfusion requirements and incidence of postoperative complications, particularly bile leaks and subphrenic collections, are higher in jaundiced patients than in controls, but comparable to those reported in patients with biliary obstruction subjected to PBD. There is no evidence that PBD can reduce the rate of these complications.

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REFERENCES


ARCHIVES OF INTERNAL MEDICINE

Higher Risk of Venous Thrombosis During Early Use of Oral Contraceptives in Women With Inherited Clotting Defects
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Background: Results of recent studies show that the risk for venous thrombosis is highest during initial oral contraceptive use. This suggests a subgroup of females who are at immediate risk of thrombosis when exposed to oral contraceptives.

Objective: To determine whether women with inherited clotting defects who use oral contraceptives develop venous thrombosis at an earlier stage than do those without inherited clotting defects.

Methods: Analysis of the data from the Leiden Thrombophilia Study, a population-based case-control study with data on duration of oral contraceptive use and recently detected genetic coagulation disorders. Patients had a first episode of objectively proven deep vein thrombosis. Patients and controls were considered thrombophilic when they had protein C deficiency, protein S deficiency, antithrombin deficiency, factor V Leiden mutation, or prothrombin 20210 A mutation.

Results: Risk of developing deep vein thrombosis was greatest in the first 6 months and the first year of oral contraceptive use. Compared with prolonged use, the risk of developing deep vein thrombosis was 3-fold higher in the first 6 months of use (95% confidence interval [CI], 0.6-14.8) and 2-fold higher in the first year of use (95% CI, 0.6-6.1). Patients who developed venous thrombosis in the early periods of use were more often thrombophilic. Among women with thrombophilia, the risk of developing deep vein thrombosis during the first 6 months of oral contraceptive use (compared with prolonged use) was increased 19-fold (95% CI, 1.9-175.7), and in the first year of use, it was increased 11-fold (95% CI, 2.1-57.3).

Conclusions: Women with inherited clotting defects who use oral contraceptives develop venous thrombosis not only more often but also sooner than do those without inherited clotting defects. Venous thrombosis in the first period of oral contraceptive use might indicate the presence of an inherited clotting defect. (2000;160:49-52)

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