SURGICAL TREATMENT OF GALL-BLADDER CANCER

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There are over 1000 new cases of gall-bladder cancer noted in Poland each year. They account for about 0.17% of all cancers in males and about 0.5% of all cancers in women. Both occur most often in elderly people between 6 and 7 decade of life, by far the more common for women. Despite the relative rarity of this cancer, it is the sixth among men and fourth among women, most common type of malignant tumors of the digestive system (1). The disease is usually diagnosed in an advanced stage, which combined with aggressive tumor biology and lack of efficient systemic therapy, results in only a several month survival from diagnosis. Therefore, till today, the approach towards the treatment of gall-bladder cancer was characterized by a high level of nihilism. However, data obtained from centers which specialize in hepato-biliary surgery, show that aggressive surgical approach allows long term survival for some patients. That is why a radical resection is currently the method of choice in the treatment of this disease. Unfortunately, only a scarce number of patients can be considered for radical surgical treatment, resulting in rates as low as 15-47% depending on the data from literature. The role of other forms of therapy is limited and requires further clinical studies.

According to the NCCN (National Comprehensive Cancer Network) guidelines, only palliative chemotherapy based on gemcitabine and cisplatin has been placed in the first category when it comes to the strength of recommendations. The role of adjuvant chemotherapy or chemo-radiotherapy (adjuvant and palliative) is still not clearly defined (2). The prognosis mainly depends on the stage of the disease at the beginning of treatment.

Considering the fact, that in 0.3-1% of excised gall-bladders, pathological examination reveals cancer, in practice we deal with very different clinical conditions. Their spectrum includes the earliest stages of incidentally discovered cancers, and those which are manifested as locally unresectable and/or disseminated disease. There is also an intermediate group of tumors which were discovered in postoperative histopathological examination that present a more advanced stage than T1a, tumors discovered incidentally during cholecystectomy performed for non-cancer related reasons and suspected cancers on the basis of preoperative tests and pre-judged to be resectable (3). Patients with confirmed or suspected gall-bladder carcinoma require very precise radiological diagnosis based on a multislice, spiral computed tomography and magnetic resonance imaging. They allow us to determine the degree of loco-regional advancement of the disease and above all, to illustrate the possible presence of distant metastases, which exclude the possibility of radical treatment. According to various reports, PET (Positron Emission Tomography) tests are gaining the importance as it results in a 25-50% detection of clinically unsuspected disseminated process. The diagnostic role of laparoscopy is not yet clearly defined, however in case of advanced tumors (> T2) seems to be a valuable option, allowing to recognize intraperitoneal dissemination through a minimally invasive approach, and thus protect the patient from an unnecessary
Surgical treatment of gall-bladder cancer

laparotomy (3-8). The evaluation is based on the TNM staging system for gall-bladder carcinoma (tab. 1). Very popular is Nevin’s classification as well (tab. 1= (9, 10).

HISTOPATHOLOGICALLY CONFIRMED CANCER

T1 Stage

T1a stage cancers (infiltration limited to the mucosa) require only a cholecystectomy, provided that the margin of the cystic duct is free from cancer. The prognosis for this group of patients is very good and according to some reports a 5-year survival reaches 100%. The approach to tumors with T1b stage stirs controversy. A number of publications report a 5-year survival rate of up to 90% after cholecystectomy alone; however on average in 10% of cases a persistent tumor in the gall-bladder fossa can be found. The frequency of metastases to regional lymph nodes can reach 20%. In the material of MSKCC (Memorial Sloan Kettering Cancer Centre) cancer tissue was found in even up to half of patients with T1 tumors (including pT1a and pT1b). Therefore at this stage of advancement most of authors recommend radical surgical re-intervention (2, 3, 6, 11, 12).

T2-T3 stage

Similarly in case of T2 and T3 tumors, radical surgery is the preferred treatment. In the material from MSKCC in specimens re-

Table 1. AJCC TNM staging for gall-bladder cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1s</th>
<th>N0</th>
<th>M0</th>
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<tbody>
<tr>
<td>0</td>
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<td>I</td>
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<td></td>
<td>any T</td>
<td>N2</td>
<td>M0</td>
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<td></td>
<td>any T</td>
<td>any N</td>
<td>M1</td>
</tr>
</tbody>
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Table 2. Nevin’s classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>infiltration of mucosa</td>
</tr>
<tr>
<td>II</td>
<td>infiltration of muscularis layer</td>
</tr>
<tr>
<td>III</td>
<td>transmural infiltration</td>
</tr>
<tr>
<td>IV</td>
<td>lymph node metastases</td>
</tr>
<tr>
<td>V</td>
<td>liver invasion, locoregional and/or distant metastases</td>
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</tbody>
</table>
moved during re-intervention tumor tissue was found in 61-85% of cases with T2 and T3 tumors, respectively. Radical surgical treatment allows a 5-year survival rate of up to 80% (T2N0), which is more than double comparing to the simple cholecystectomy. In case of T3 tumors survival rate ranges from 20-60% (3-8, 13, 14).

T4 Stage

The majority of T4 tumors are unresectable and eligible for palliative treatment. Exceptions are tumors located in the main trunk of the portal vein and/or infiltrating several surrounding organs, which may be removed „en-bloc”. Although the procedures are technically feasible and in literature we can find cases with long-term survival after such extensive interventions, qualification for that kind of treatment must be done with extreme care. They carry a serious risk of death and complications. Their value is not clearly defined, although there are reports where 5-year survival rate reaches 15-20% (4, 15, 16).

THE TUMOR FOUND DURING LAPAROSCOPIC CHOLECYSTECTOMY OR DURING THE INTRAOPERATIVE PATHOLOGICAL EXAMINATION OF THE REMOVED GALL-BLADDER

If the gall-bladder tumor is found during the procedure and the surgeon is experienced enough in hepatobiliary surgery, a laparotomy and radical surgery should be performed. Before the resection, the peritoneal cavity should be carefully examined and an intraoperative liver ultrasound examination should be performed in order to assess the extent of invasion and exclusion of distant metastases. The attempt of continuing laparoscopic surgery is contraindicated and may lead to perforation of the gall-bladder wall and the spillage of bile into the abdominal cavity (15-45% of patients) which tends to result in dissemination and significantly worsens the prognosis. For the same reasons it is not recommended to run biopsy and perform cholangiography, although this option is allowed for a histological verification before extending the procedure. In case of abnormal mass in removed gall-bladder the specimen should be histopathologically examined and then radical surgery should be performed. Surgeons without experience are expected to finish the procedure and transfer the patient to a referral center. Concerns about worsening prognosis of patients treated in stages (cholecystectomy, followed by radicalization as step two) cannot be justified in the light of current data, provided there is no damage to the gall-bladder wall at the time of cholecystectomy. However, if the cancer is suspected at an early stage of the procedure, if resection R0 cannot be performed the gall-bladder should be left untouched (3, 4).

THE TUMOR DETECTED OR SUSPECTED PREOPERATIVELY

Additionally to thorough medical imaging, many surgeons recommend diagnostic laparo-

![Fig. 1. Advanced gall-bladder cancer](image1)

![Fig. 2. Advanced gall-bladder cancer (after specimen removal)](image2)
copy, as even in potentially resectable tumors (T3 and rarely T4) an unexpected intraperitoneal dissemination can be detected in 60-80% of cases. Due to the high risk of the generalized cancer spread, PET gains importance as it allows detecting a large proportion of patients with systemic disease. This eliminates the possibility of radical surgery. Given the risk of damaging the gall-bladder wall during laparoscopy it is recommended, if possible, to perform a priori a laparotomy with a radical resection if possible (3, 7). In patients with obstructive jaundice as a primary symptom of gall-bladder cancer usually palliative endoscopic biliary drainage is a definitive treatment. Jaundice in these patients, most commonly is related to the extensive infiltration of the bile ducts in the hepatoduodenal ligament and/or multiple liver metastases. Cytoreductive operations in this situation if possible, rarely improve the fate of the patient. In the era of endoscopy, bilioenteric Roux-Y anastomosis with isolated segment III or V bile ducts also lost its importance. However, these operations may improve the quality of life in selected patients. (17)

THE EXTENT OF RESECTION (FOR ALL STAGES)

Radical surgery of gall-bladder cancer is a highly complex procedure and should always be carried out at the center with extensive experience in hepatic and biliary surgery. Mortality ranges from 0-30%, and the complication rate is 20-67% (8). The aim of the surgical treatment is a radical resection R0. An analysis of material from leading centers (MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center) show that the prognosis depend largely on the stage of the disease (based on TNM classification) and tumor biology. Therefore, in recent years there has been a gradual turn from a routine of very extensive, multi-organ resections. Nowadays it is preferable to perform procedures which are more tailored to the intraoperative stage of the disease. Studies show that a 2 cm liver margin around the healthy gall-bladder fossa/tumor is sufficient, therefore nonanatomical resection of segments V and IVb is usually adequate for patients with cancer detected accidentally. Routine performance of extended resections such as hemihepatectomy although still has its supporters, has no rational justification and does not translate into an increased survival rate and does not translate into an increased survival rate, as they are also one of the factors increasing the number of postoperative complications (3, 11, 14). Due to the high risk of lymph node metastases (>40% for stages T2 and above) it is required to perform lymphadenectomy. Lymph node involvement is one of the most important prognostic factors and plays a key role in the assessment of prognosis.

According to the NCCN guidelines lymphadenectomy should include the lymph nodes of the hepatoduodenal, hepatogastric ligaments and retroduodenal (2). It is necessary for proper staging to remove minimum three lymph nodes, although recent reports suggest that examining at least six nodes allows assessing correctly the nodal status (18). The presence of metastases in the lymph nodes outside the hepatoduodenal ligament, especially para-aortic (seized in approximately 20-30% of cases), is usually associated with systemic disease and inability in achieving a long-term survival, even after the most radical resection. Therefore some authors recommend to begin the procedure with an assessment of the para-aortic area and remove a sample of lymph nodes for frozen section, and possible withdrawal from the resection in case of confirmed metastases. Routine excision of extrahepatic bile ducts is not recommended. Studies show that it neither increases the completeness of lymphadenectomy nor improves the prognosis, furthermore it has a negative impact on the outcome and number of complications.

Duke University’s material shows that in patients who had their extrahepatic bile ducts removed, serious complications occurred in 67%. Complications were observed in only 10% of cases if the extrahepatic bile ducts were not resected. Resection should be performed in
case of a positive margin of the cystic duct. Bile ducts should also be removed when necessary to achieve the radical resection (R0), e.g. in the case of direct invasion (3, 8, 11, 14, 19). In addition, it is recommended to resect portal sites during reoperation, although recent reports doubt the advisability of routine use of this procedure. The presence of tumor implants at this location is rather exponent generalization of the neoplastic process; therefore, this element has no effect on the natural aggressive course of the disease (20).

In the case of T1b stage tumors, some authors suggest only to perform lymphadenectomy of the hepatoduodenal ligament without hepatic resection, as the procedure doesn’t conclude a clear and proven advantage over simple cholecystectomy (21). Some centers described the successful use of laparoscopic resection for T2 tumors. However the number of operated patients is small and it is hard to explicitly assess this as to date, controversial form of therapy (22, 23). Some Japanese authors advocate to plan the extent of resection based on the depth of subserosal infiltration (SSI). They advise to restrict the treatment to cholecystectomy and lymphadenectomy in cases with the minimal infiltration (SSI min), performing hepatic resection, lymphadenectomy and biliary excision if the deeper layers are infiltrated (SSI med and mas) (24).

It is much more difficult to perform a radical surgery in advanced cases. Advanced carcinoma of the gall-bladder may extensively infiltrate the liver parenchyma, hepatoduodenal ligament and the adjacent organs (duodenum, colon). In the absence of generalized dissemination of the disease, some surgeons perform a multi-organ resection. They are justified only if a radical procedure can be achieved. The R0 resection is the main prognostic factor for a 5-year survival. In view of the frequent need for extensive liver resection (extended right hemihepatectomy), where the volume of unresected liver parenchyma (FLR-Future Liver Remnant) is <25-30%, it is recommended to embolize the right portal vein (PVE-Portal Vein Embolization). An additional benefit of this technique is that the interval between a PVE and a resection allows selecting the group of patients which will develop a rapid progression of the disease, and therefore would not benefit from surgery.

Worth noting is PVE alone can stimulate tumor growth and thus contribute to the progression of the disease, excluding the possibility of a radical surgery. It is often necessary to perform the reconstruction within the vascular system (especially the portal vein) and to widen the surgery by resecting the surrounding organs, with a pancreaticoduodenectomy included. Although tumors that require such an extensive resection usually coexist with the distant metastases, the small group of patients with regional disease may benefit from this procedure. In the literature is described long-term survival after such procedures (3-8, 14, 15).

PROGNOSTIC FACTORS AND SURVIVAL

Prognosis depends mainly on the stage of the disease and the possibility of R0 resection. The tumor biology seems to play a key role and it largely determines the course of the disease. The least advanced cancers (T1a) allow for almost a 100% 5-year survival after only laparoscopic cholecystectomy. In advanced stage tumors the chance to perform radical surgery decreases which worsening prognosis, without the possibility of a 5-year survival in the majority of patients with T4 and the R1/R2 resections. Therefore, patients with incidentally detected cancer have significantly better prognosis than patients with cancer diagnosed on clinical symptoms. Significant is the presence of residual disease in patients re-operated on prior cholecystectomy. According to the data from John Hopkins University a 5-year survival rate decreased from 84.8% in patients without persistent disease to 36.9% in patients whose postoperative pathological assessment revealed the presence of cancer cells in the resected specimen. A similar relation was also observed in the case of lymph node metastasis. This reduced the 5-year survival from 72.9% to 26.5%. In the D’Angelica material from MSKCC, in the N1 stage a decrease of 5-year survival rate from 51% to 17% (N0) was observed. Many authors emphasize the fact that the extent of resection is not an independent prognostic factor. Therefore, routine expanding of surgery towards major liver and bile ducts resection does not improve the results of treatment. Resections like this are only justi-
fied if there is a possibility of performing a complete microscopic excision (11, 13, 14).

THE ROLE OF ADJUVANT THERAPY

There is no conclusive evidence to support the efficacy of adjuvant therapy such as chemotherapy or chemo-radiotherapy, although new treatment regimens based mainly on gemcitabine arouse hope. NCCN recommendations suggest consideration of postoperative chemo-radiotherapy (with the exception of T1b stage) or chemotherapy based on derivatives of fluoropyrimidines and gemcitabine. Only in the palliative setting chemotherapy consisting of gemcitabine and cisplatin has recommendation, which is based on prospective, randomized clinical trials (2). The use of preoperative chemo-radiotherapy brings some hope. Authors from India have used this method in three patients, whom all showed significant response to the treatment. In two patients who underwent therapy followed by surgery, in one case there was a pathological partial response, thus in the second patient a postoperative histopathological analysis of the specimen showed minimal residual cancer. A small number of patients treated using this method obviously does not allow to draw any far-reaching conclusions, however, the initial results are encouraging, and without any doubts it should be tested on a larger number of patients (25).

SUMMARY

Despite the aggressive nature and poor prognosis of gall-bladder cancer there is a group of patients who can achieve significant benefits from a radical surgical treatment. The possibility of obtaining long-term survival, even in case of patients with locally advanced cancer and metastases to regional lymph nodes, prompts to verify nihilistic approach to the treatment of this disease. Obviously such therapy can and should be performed only in centers specializing in hepatobiliary surgery. Due to the high recurrence rate, most of which are systemic, the hope of improving treatment outcomes should be sought in the use of combination therapy, based on a new chemotherapy and chemo-radiotherapy regimens with the addition of targeted therapy (26). Unfortunately, the current application of these methods did not bring the expected benefits.

REFERENCES

14. D'Angelica M, Dalal KM, DeMatteo RP i wsp.: Analysis of the extent of resection for adenocarci-