T2 gall bladder cancer: optimal management according to location of tumor (T2a or T2b)

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Lecture : T2 in gall bladder cancer (GBC) is involvement of the perimuscular connective tissue (vs. T1b, which is involvement of the muscularis propria and T3, which is involvement of the serosa).
Recently, T2 tumors on the hepatic side (T2h) of the gall bladder (GB) have been differentiated from those on the peritoneal (serosal) side (T2p). In a 4-institutional study including 252 T2 GBCs, 99 were classified as T2h and 153 as T2p - vascular invasion (51% vs. 19%), neural invasion (33% vs. 8%) and lymph node metastases (40% vs. 17%) were more common in T2h vs. T2p lesions. Recurrences in liver and lymph nodes were more frequent (23%, 16% vs. 3%, 3%) and 3 year and 5 year survival were less (52%, 43% vs 74%, 65%) in T2h vs. T2p lesions (Shindoh. Ann Surg 2015;261:733-739). The 8th edition (2017) of the AJCC/ UICC TNM classification differentiates a T2 lesion on the peritoneal (serosal) side (T2p) which is classified as T2a from one on the hepatic side (T2h) of the GB which is classified as T2b. T2aN0M0 is classified as stage IIA and T2bN0M0 as stage IIb; T2N1M1 is stage IIIa and T2N2M0 is stage IVB. This subclassification of T2 into T2a and T2b has been validated in a recent retrospective analysis of 60 T2 patients (Wang. Oncol Lett 2018;16:4427-4433).
Majority of T2 GBCs can not be detected preoperatively on imaging and are incidental GBCs i.e. diagnosed postoperatively on histopathological examination of the GB removed with a preoperative diagnosis of gall stone disease. Some of these lesions can be detected if the GB is opened and carefully examined by the surgeon on the operation table itself and submitted to frozen section histopathological examination for any suspicious area (e.g. ulcer, nodule or thickening). If an early GBC (no liver infiltration), is diagnosed preoperatively on ultrasound, the extent of the tumor should be confirmed with a good quality contrast enhanced computed tomogram (CT); an endoscopic US (EUS) better delineates the extent of local infiltration but it may still be difficult to differentiate a T2 lesion from T1b or T3. Even when it is an incidental GBC diagnosed postoperatively on histopathological examination, differentiation between T2 and T3, especially on the hepatic (non-peritoneal/ non-serosal) side, is not easy and requires expertise on the part of the pathologist.
Simple cholecystectomy alone is associated with low (25%-40%) 5 year survival whereas extended (radical) cholecystectomy gives higher (40-60%) 5 year survival in T2 GBC. There is no difference between liver wedge (n=55) and segment IVb+V (n=30) resection in T2 GBC (Horiguchi. J HBP Surg 2013;20:518-524). Extended cholecystectomy can be safely performed laparoscopically (Han. Dig Surg 2019;36:1-6) also; care, however, should be taken to avoid GB perforation and bile spill.
Subanalysis in a recent report showed equal 5 year survival (69% vs. 74%) after simple and extended cholecystectomy in node negative T2 (T2N0) patients (Lee. J Korean Med Sc 2018;33:e186) but it is virtually impossible to differentiate between N0 and N+ patients preoperatively. Residual disease is found at reoperation in 30-60% of the patients with T2 incidental GBC (Creasy. J GI Surg 2017;21:1254-1261). It is not possible to find out which patients with incidental GBC do and which patients do not have residual disease; all patients with T2 incidental GBC should, therefore, be offered the benefits of reoperation for completion extended cholecystectomy (CEC). Before reoperation, repeat US, chest X-ray, CT (chest, abdomen and pelvis), PET scan and staging laparoscopy should be performed to exclude any distant metastases. As for the timing of the reoperation, best results were obtained when reoperation was performed 4-8 weeks after the index cholecystectomy (Ethun. JAMA 2017;152:143-149). Lymph node metastasis is seen in as many as 30-50% of T2 GBC; a lymphadenectomy is, therefore, a must to obtain R0 resection status in T2. An analysis of 192 patients with T2 GBC revealed that hepatic resection was not necessary in patients with peritoneal side (T2a) tumor (Lee. Surgery 2017;162:515-524). On the other hand, some other reports have suggested no liver resection i.e. simple

cholecystectomy with lymphadenectomy alone, because liver resection did not improve survival in hepatic side (T2b) tumors (Park. Ann Surg Treat Res 2018;94:135-141).

Recurrence is more common in patients with lymph node metastasis and recurrences are more commonly systemic; adjuvant chemotherapy is, therefore, recommended in node positive T2 (T2N+) patients. In addition to T and N stage, consideration should also be given to histological features e.g. differentiation, peri-neural invasion (PNI), lympho-vascular invasion (LVI) and peri-capsular invasion (PCI). Preoperative CEA, CA 19-9 and IL-6 levels (Wang. J Surg Oncol 2018;117:1672-1678) also indicate risk of recurrence, prognosis and survival. Recurrences (loco-regional or metastatic) in GBC are very common, even after intent-to-cure surgical resections and even in the early stages of the disease. Recurrences in GBC are very rarely amenable to surgical resection and usually indicate a terminal stage of the disease.

The Author has advocated an 'Indian Buddhist middle path' (Kapoor. J HBP Surg 2007;14:366-373) i.e. aggressive surgical approach for early (mostly incidental) GBC and palliative non-surgical approach for advanced (unresectable or resectable but likely incurable) GBC. The Author disagrees with some of the recent reports which advocate a lesser procedure than extended cholecystectomy for T2 GBC and is of the opinion that T2 GBC, which is highly and eminently curable, should receive an aggressive approach in the form of a proper and complete extended (radical) cholecystectomy including both liver wedge and lymphadenectomy to reduce the risk of recurrence and improve the survival with a hope for possible cure.

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