Drs. Abi-Rached and Neugut have presented a comprehensive review of the natural history and epidemiologic characteristics of patients who develop carcinoma of the gallbladder. They correctly point out that this tumor is a rare neoplasm, with the annual incidence in the United States being quite low; the number of patients dying from gallbladder cancer in 1978 was estimated to be 2,469, representing only .3% to 1.0% of total cancer deaths in the United States [1]. Since incidence rates vary significantly by geographical area, the risk factors associated with this tumor are of interest. For example, in Chile, cancer of the gallbladder and bile ducts accounts for 5.25% of cancer deaths [2]. Among Jews in Israel, the incidence appears to be higher in patients of European birth compared with those born in Asia [3]. Incidence also appears to be higher in Native Americans and Mexican-Americans born in the United States than in other population groups in the United States [4]. For instance, gallbladder cancer is the most common gastrointestinal malignancy among Southwestern Native Americans [5].

As Drs. Abi-Rached and Neugut indicate, in all of these groups the incidence of this disease is higher in women than in men. In Mexico City, this neoplasm is the fourth most common tumor found in women [6]. Whether estrogen and/or progesterone play a role is unknown, though it has been postulated that oral contraceptive use or menopausal estrogen therapy may be associated with an increased risk of nonmalignant gallbladder disease [7].

Etiology
In spite of these epidemiologic observations, the etiology of gallbladder cancer remains obscure. The various risk factors identified have included sex, age, cholelithiasis, occupational exposure, diet, and chronic irritation [6]. Biochemical factors may also play a role in biliary tract carcinogenesis, since bile contains a complex mixture of chemicals. Studies on the biochemical content of gallstones and bile have suggested that increased concentrations of lithocholic acid or glycolithocholic acid may act as carcinogens [8]. The geographical variations observed may reflect cultural, dietary, and/or genetic differences between populations. Therefore, studies of both geographic differences and the biochemistry of bile may be useful in ultimately determining the etiology of this cancer.

Presentation, Diagnosis, and Treatment
The diagnosis and clinical presentation of this neoplasm are quite protean. Most frequently, the diagnosis is made at the time of surgery. The staging and patterns of spread are clearly defined, with the presence or absence of direct invasion of adjacent organs being the most important prognostic factor.

The therapy of a rare tumor such as gallbladder cancer is based on previous reports in the literature, with little or no prospective data available. The overall survival of these patients is quite poor, with 5% surviving more than 5 years. The issue of which type of surgical management is most appropriate was analyzed in detail by the authors, and no consensus on a uniform approach emerged from their analysis. It does appear that the type of surgery can be based on the stage of the tumor, with invasive tumors requiring more radical approaches. Examination of data relating to
patterns of failure after attempts at curative surgery [9] demonstrates that local and/or regional failure occurs most commonly in the gallbladder fossa and porta hepatis area. Therefore, it appears that even radical surgery may not prevent this type of recurrence.

**The Role of Radiation Therapy**

The role of radiation therapy in treating this tumor is also reviewed by the authors. As they point out, data are quite sparse. It has been proposed that adjuvant postoperative radiation therapy might prolong; however, data to support this are lacking. Certainly, we should consider clinical trials of combined modality approaches, such as those being used in other gastrointestinal neoplasms, to determine whether adjuvant postoperative radiation therapy might benefit outcome. Because of the rarity of this tumor, such trials would require multi-institutional participation, perhaps with the help of the cooperative groups.

**Chemotherapy**

The role of systemic chemotherapy in gallbladder cancer also is undefined. Anecdotal reports in small populations of patients have indicated that objective responses may occur, but overall, no data have emerged demonstrating clearly that single agents or combinations of agents are useful. In vitro studies [10] have demonstrated that several chemotherapeutic agents may have antitumor activity, including carmustine, cisplatin (Platinol), vinblastine (Velban), mitoxantrone (Novantrone), and methyl-glyoxalbisguanylhydrazone (MGBG). Certainly, therefore, phase II studies would be appropriate to measure the response of gallbladder cancer to these or newer agents. Again, because of its rarity, this will require a cooperative group approach. Regional intra-arterial chemotherapy has been explored for unresectable gallbladder cancer. However, only small groups of patients have been treated, and the results remain anecdotal.

**Conclusion**

In conclusion, the article by Abi-Rached and Neugut is a comprehensive review of the clinical features and therapeutic options available for patients with gallbladder carcinoma. The epidemiologic and biochemical studies are of interest, and may ultimately provide information on the etiology of this tumor. The authors correctly point out that the management of these patients is predominantly surgical, though an operation of choice has not been determined. The clear message from this review is that a disease such as gallbladder cancer would benefit from a systematic approach in a cooperative group setting.

**References:**


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