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GUEST EDITOR COMMENT

Gallbladder Cancer

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Gallbladder cancer (GBC) has attracted less attention than other hepatobiliary carcinomas from the medical fraternity due probably to being rare in the western world. In this region of the world, North India, it has emerged, in last twenty to 25 years, as the third common cancer and a cancer of hopeless prognosis without effective surgical treatment and resistant to chemotherapy as well as radiotherapy. In my clinical practice the patients diagnosed with GBC were relegated to palliative care team till about 10 years ago. Greater awareness of the increasing incidence of diagnosis of GBC and emergence of hepatobiliary and pancreatic services has focused our attention to gallbladder cancer more than before. In the year 1980 there was no publication of GBC from our Institute whereas in 2005 there were as many as ten publications emanating from the same unit.

There is no reason to be happy about the clinical situation of GBC because of the present greater awareness and heightened clinical response to patients of gallbladder cancer. The fact of the matter is that the cases are continuing to be seen in advanced inoperable stage of their disease with overall 5 years survival rate of less than 10% and a median survival of 6 months.

This situation, however, is present across the globe where GBC is prevalent. GBC has very strong geographical predilections, being common in North and Central India, areas of Japan and Korea, Central and South America, Eastern Europe and Israel. This strong affinity to geographical areas indicates environmental factors at the root of genesis of GBC. Yet the dietary habits, life styles and weather conditions are vastly different in these geographic confines. There is much work to be done to work out the etiology of gallbladder cancer.

In planning of this seminar I have taken the experts help from imminent clinicians from the high incidence areas and drawn on their vast experience to present some of the available material at this moment of time in the ongoing evolution on understanding and treatment of GBC. A hit in Pub Med for GBC reveals 5,142 publication so far till end of 2005 for GBC. As an eye opener for the same period there are 159,098 publications for breast cancer, 145,058 for lung cancer and 1,814,944 for cancer cervix. A substantial amount of work is to be done to unravel the GBC mystery.

The global perspective of GBC is brought out by Professor V.K. Kapoor from Sanjay Gandhi Postgraduate Institute in Lucknow in North India. He argues for more work in the aspects of non-stone GBC and the cause of greater prevalence of this type of GBC in Japan and role of female sex hormones as GBC is commoner in the female than male sex. From my own department the work done in the aspects of demography started by J. Ram Kumar in 1998 and continued by Rohan Sinha, Mallika Tewari, and Arundhati Rai under guidance from Professor S.C. Mohapatra of Department of Community Medicine reveals strong female preponderance and the patients are characterized by young age, rural background, low socioeconomic status, bearing many children and away from the amenities of modern medicine. There is universal observation that GBC is diagnosed late in the evolution of the disease. Recognition and detection of the preneoplastic lesions of gallbladder could give an opportunity for diagnosis of GBC in early stage.

The association of preneoplastic lesions with GBC is discussed by Ivan Roa's team from Chile, another high incidence area. Their observation of dysplasia-carcinoma sequence as the most plausible carcinogenic pathway leading to GBC in a time span of approximately 10 years offers greater understanding of pathogenesis of GBC. Ivan Roa's team further evaluates the close relation gallstones have with GBC since 70–90% GBC is associated with gallstones. Large size and multiplicity

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of gallstones' closer association with GBC may point towards the carcinogenic potential of gallstones as well as their significant bystander status while some other carcinogen is at work. It is observed that 10% GBC has no stones and in Japan non-stone GBC is commoner than elsewhere, an observation emphasized by V.K. Kapoor in the first article. But it is the 'silent' gallstone that perhaps requires wide based research work to fix the contribution of silent gallstone to development of GBC. This is reviewed comprehensively by Dr. Mallika Tewari but at the present level of evidence Dr. Tewari is unable to emphatically advise cholecystectomy for silent gallstone. As a compromise she advises cholecystectomy for silent gallstones in high incidence areas, in older patients. In conclusion she considers all silent stones to be really not silent as they continue to produce different degrees of morphological changes in gallbladder although not causing symptoms.

If not the stone than infection or stone with infection may be the most likely cause of GBC. This is argued with strong data by Professor Sandeep Kumar of King George's Medical University, Lucknow. Professor Sandeep has strong links to statistical teaching and he argues almost convincingly that stone-particularly mixed stones and infection are probably the cause of GBC. That both these could be related to low social background of most of the patients further strengthens the observation since infection is more prevalent in low socioeconomic strata of proportion. Another dimension of carcinogenic agents that might be causing GBC is added by Dr. Manoj Pandey from Bhopal in Central India. Dr. Pandey worked in the famous Regional Cancer Centre in Thiruvananthapuram for several years at the very southern tip of India. Conversely GBC is extremely uncommon in Thiruvananthapuram and this has given Dr. Pandey a clear and unbiased view of what may be causing GBC and he points his finger to environmental pollution particularly with heavy metals. Dr. Pandey has recently shifted to my own Department in IMS, BHU, and he has taken research on carcinogenesis of GBC with the seriousness it deserves.

Beside stone, infection and heavy metals the answer to genesis of GBC may be found at the molecular level. Angelica A. Saetta from Department of Pathology, University of Athens demonstrates that 'accumulation of genetic alterations,' though their sequence is unclear, may be responsible for GBC, and advises further characterization of the molecular events specific to GBC. This delineation, she feels, will give an opportunity for better diagnosis and clinical management of the patient at present beset with late presentation world wide. Can the modern imaging methods help in diagnosing GBC early is the problem addressed to in their comprehensive article by Dr. Antonio Rodriguez-Fernandez and his colleagues from University Hospital of Granada, Spain. The modern imaging methods: ultrasound, CT, MRI, and functioning imaging with PET has been extensively studies and commented. Dr. Fernandez advises that PET-CT equipment that allows fusion of structural and functional images and the use of biological probes are likely to transform the imaging diagnosis of GBC but the 'human factor' of greater awareness will continue to be of much importance.

If not the modern imaging methods then tumor markers may point to the diagnosis of GBC. There is general paucity of data on tumor markers for GBC. CEA and CA 19-9 do not give a strong and specific result for GBC. In her innovative research Amita Chaube, PhD fellow under Professor Usha of the Department of Pathology in collaboration with my own department, has presented, yet unpublished data, on CA 125, as a potential tumor marker for early detection of GBC, at 11 μ/ml level and in correction with clinical features.

As diagnosis of GBC in made at late stage in majority of the patients, there is a wide spread feeling of nihilism to offering surgical treatment. Professor Sikora, of Sanjay Gandhi Postgraduate Department of Surgical Gastroenterology, Lucknow strongly argues that pattern of locoregional spread of the disease should dictate the surgical procedure. Radical surgery improves survival but long term benefit of aggressive surgery for advanced disease requires to be weighted against the associated high mortality and morbidity.

The new mantra in treatment of gallstone is laparoscopic surgery (LC) comprehensively commented by Dr. Mac-Andre Reymond and his team of surgeons from Evangelic Hospital, Bielfield, Germany. There is overenthusiastic use of LC in gallbladder disease. Although the long term effect of initial LC versus open cholecystectomy (OC) on the prognosis of patients with GBC remains undefined, any patient suspected to have GBC should not be operated by LC. To guard against inadvertent LC for GBC bearing GB Dr. Raymond advises prevention of bile spill and bagging of gallbladder at the time of retrieval. In spite of all the precautions of surgery for GBC there are situations when the diagnosis of GBC is missed at the primary surgery raising important question of type and form of further treatment.

Professor Mahesh Misra and his team from All India Institute of Medical Sciences, New Delhi, India has discussed the problem of GBC found as surprise on the resected gallbladder specimen. Their advice, based on extensive literature review and personnel experience is not to do anything in stage Ia and re-operation for patients in stage Ib, II, and III at the earliest time following the discovery of GBC on gallbladder specimen. In the re-operation a more radical approach is followed that includes excision of all port sites, extended operation of

gallbladder area and lymph node dissection. Professor Misra argues that greater awareness is the key to application of appropriate treatment for GBC, a feeling expressed uniformly by all the clinicians.

There is repetition of facts in these three surgical articles by Professor Sikora, Professor Raymond and Professor Misra. These repetitions are in perspective to different arguments being given by the authors. Therefore we have not applied any editorial modification of the arguments to maintain the originality and perspective of the authors.

We look forward to chemo-radiotherapy to improve the survival of gallbladder cancer that are locally advanced, recurrent or have or suspected to have residual disease and to down-stage the disease preoperatively. Dr. Aretexbala and his team of clinicians from Department of Oncology, Clinica Alemana Santiago, Chile have addressed to this problem. Due to the rare nature of the disease in western world there is little or no research on design and protocol development of chemotherapy regimens for GBC. Good clinical effect of Gemcitabine and Cisplatin on cancer pancreas has been extrapolated to GBC. But there is overall lack of good data on dose, concurrent use of radiotherapy and drug associations in GBC. There is a wide field in evolution and evaluation of chemotherapy regimens and radiotherapy waiting for GBC.

It is a natural sequel of advancing GBC, even though clinically not apparent, to tax on the bodily nutritional status. In their interesting paper Arundhati Rai and coworkers under the overall guidance of Professor S.C. Mohapatra at IMS, BHU have reported worsening of not only anthropometric data but also of biochemical parameters of nutrition. Overall a state of anorexia, progressive depletion of calorie reserve, body fat and muscular tissue is produced. This situation renders the patient even more untreatable than the locally advanced nature of the disease. Building up the nutrition by enteral or parenteral route produces another dimension in the treatment making it even more costly.

This special issue is a result of international effort where every one has helped to bring out the edition. I am very grateful to each and every one of my authors for their ready cooperation, help and advise from time to time and above all their wonderful contribution that will enrich world data on GBC. In the beginning when Professor Temple wrote me inviting for this issue I could not comprehend the honor he was bestowing on me by inviting me to edit the Seminars in Surgical Oncology for the subject of cancer gallbladder. I am very grateful to Professor Temple for this. Ms. Anjita Pandey MSc (Zoology), my PhD scholar has done all that is required to arrange the manuscript, correspondence and final product. I thank my former students for the tribute.