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From the Desk of Director Research

Hepatocellular carcinoma (HCC) remains one of the most common malignant tumors in Asia. Today, there is an array of therapeutic modalities available to the patients with HCC. However, surgery, be it resection or liver transplantation, offers the only hope of long-term disease free survival for these patients. "Special Feature" of this issue highlights "Hepatocellular Carcinoma- An Update." The Institute is grateful to Dr A S Soin, Chairman & Chief, Liver Transplant & Hepatobiliary Surgeon, Medanta - The Medicity, Gurgaon for providing the 'Guest Article' on "Liver Transplantation for Hepatocellular Carcinoma".

There is a high prevalence of gall bladder cancer in the Gangetic basin of North India. Majority of the patients present with locally advanced or metastatic cancer, which is incurable and treatment options are extremely limited. Advances in imaging of hepato-biliary malignancies are helping the clinicians in quick decision making and offering timely treatment strategies to the patients. "Perspective" in this issue profiles 'Role of Imaging in Hepato-biliary Malignancies' while "In Focus" covers 'Systemic Therapy of Gall Bladder Cancer'. A brief coverage of 'Recent Advances and Controversies in Thyroid Cancer' (CME & Live Surgical Workshop)-"THYROCON-2011", is also reported in this issue.

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Dr D C Doval

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This publication aims at disseminating information on pertinent developments in its specific field of coverage. The information published does not, therefore, imply endorsement of any product/ process/ producer or technology by RGCI&RC.

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SPECIAL FEATURE

HEPATOCELLULAR CARCINOMA: AN UPDATE Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancer in the world and is an increasingly common complication of chronic liver disease. About 749,744 patients suffer from liver cancer annually (GLOBOCAN 2008) and HCC accounts for 70-85% of total liver cancer. The highest incidence is in Southeastern and Eastern Asia, with a rate of 18.3-35.5 per 100,000 population, and the lowest is in central America, with a rate of 2.1 per 100,000 population. Hepatitis B virus (HBV), hepatitis C virus (HCV) related cirrhosis, hemochromatosis, and congenital metabolic diseases such as glycogen storage disease type 1, alpha-1-antitrypsin deficiency, hereditary tyrosinemia and porphyria, toxins, especially alcohol, aflatoxin B, and smoking are risk factors for HCC.

Hepatocellular carcinomais frequently asymptomatic but may present with right upper quadrant pain, weight loss, and worsening liver enzymes or, less commonly, anemia, intra-abdominal hemorrhage, or complications of portal hypertension. The diagnosis of HCC is typically established on a dynamic triple-phase contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) performed in response to an abnormal screening test or heightened clinical suspicion. The presence of characteristic vascular pattern (arterial phase enhancement with portal venous washout) is diagnostic of HCC. If there are lesions greater than 2 cm in diameter in an individual with known cirrhosis or chronic hepatitis B infection, the likelihood of HCC is high, and a diagnosis can be established in the absence of a liver biopsy if serum alfa fetoprotein (AFP) is greater than 200 ng/mL and a characteristic radiologic pattern is seen on one dynamic contrast-enhanced imaging study.

Staging

The Okuda staging system comprises of three stages, I, II and III, depending on the number of positive features out of a total of four: tumor size, ascites, serum albumin, and serum bilirubin. The CLIP (Cancer of the Liver Italian Program) staging system scores the following items from 0 to 2: Child-Pugh class, tumor extent and morphology, serum AFP and portal vein thrombosis. The AJCC (American Joint Commission of Cancer) staging system looks at whether the tumor is solitary or if there are multiple tumors, whether the tumor size is <5 cm or >5 cm, whether there is vascular invasion, regional lymph node metastasis or distant metastasis. The BCLC (Barcelona Clinic Liver Cancer) staging has become the de facto staging system (see Fig).

As per BCLC, stage 0 is very early disease, which is defined as a solitary liver cancer that measures <2 cm without tumor invasion into surrounding tissues. Stage A is early disease, when patients exhibit preserved liver



Fig: The BCLC staging system for HCC. M, metastasis classification; N, node classification; PST, performance status test; PS, performance status; CLT, cadaver liver transplant; LDLT, living donor liver transplant; PEI, percutaneous ethanol injection; RFA, radiofrequency abalation



HCC Left Lobe of Liver on CECT Abdomen function with a solitary HCC less than 5 cm in size, or up to three tumors each of which is < 3 cm in size. Patients with stage 0 or stage A disease can be effectively treated by curative therapies, such as surgical resection, liver transplantation, or by percutaneous ablation methods, including percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA). Patients with stage B (intermediate) disease can be treated with transarterial embolization (TAE) or transarterial chemoembolization (TACE). Previously, no standard systemic therapy existed for the treatment of patients with advanced (stage C) HCC; however, a randomized controlled trial (RCT) has now shown that sorafenib, an inhibitor of Rafkinase and vascular endothelial growth factor receptor, improves the overall survival of patients with stage C disease. Sorafenib is, therefore, now considered to be the standard treatment for advanced HCC. Patients with stage D (terminal) disease do not benefit from antitumor treatments and should only receive the best available supportive care.

Management

Resection: Hepatic resection is the treatment of choice for patients with HCC and preserved liver function. Even for patients with a large HCC > 10 cm in diameter, resection is safe and offers favourable long-term survival results. Indication for surgery should be determined by the size, number, and location of the tumors, the presence of vascular invasion, and the patient's liver function reserve. Liver function can be evaluated by the indocyanine green retention rate at 15 minutes (ICG R15). To be eligible for lobectomy, R15 should be < 10%. For 1/4 or removal of two segments, R15 should be < 15%. If R15 is < 25%, then only 1/8 segmentomy or removal of 1 segment should be considered. If R15 is < 35%, then only enucleation should be performed, and if R15 is > 35%, then surgery is not recommended. From a large data series from Japan with 5800 patients, the postoperative 1-, 2-, 3-, 4- and 5-year survival rates were 85%, 60%, 52%, 48% and 36%, respectively.

In recent years, laparoscopic liver resection has become feasible with the development of laparoscopic instruments that allow liver transection without major bleeding. Tumors in anterior segments or left lateral segments can be resected using a laparoscopic approach, with the benefit of less post-operative wound pain, better cosmetic result, shorter hospital stay and faster recovery.



Specimen of Left Hepatectomy

Liver Transplantation: According to the UNOS (United Network for Organ Sharing) criteria, patients are eligible to undergo liver transplant if they fall into these categories: Stage I, T1 tumor is d" 1.9 cm; Stage II, T2 single lesion measuring 2-5 cm or d" three tumors with the maximal diameter of each tumor < 3 cm. The UCSF (University of California San Francisco) criteria are: a single tumor < 6.5 cm, or a maximum of three lesions with the largest one < 4.5 cm, or cumulative size of all the tumors < 8 cm. The simple "Up-To-Seven" criteria are: seven as the sum of the size of the largest tumor (in cm) and the number of tumors.

TACE(Trans-Arterial Chemoembolisation): For patients who are not eligible for surgical intervention, TACE is the frontline treatment in most countries if they have hypervascular tumor, patent main portal vein, serum albumin>3mg/dL, total bilirubin<3mg/dL and no evidence of extrahepatic metastasis. In TACE, chemotherapeutic agents, such as cisplatin, mitomycin and adriamycin are commonly used. For embolization, gelfoam particles and lipiodol are all commonly used. The exclusion criteria for TACE/TAE are performance status ECOG (Eastern Cooperative Oncology Group)3–4, Child-Pugh Class C or Okuda Stage III, infiltrative HCC, portal vein thrombosis (main or both first branches), presence of

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marked arteriovenous shunting, peripheral artery catheterization bleeding tendency, severe cardiopulmonary illness, and allergy to intravenous contrast medium. Presence of extrahepatic metastases is a relative contraindication of TACE. In a meta-analysis of seven randomized controlled trials, the 2-year survival rate ranged from 19% to 63% in the TACE/TAE-treated groups and 11% to 50% in the control groups. The odds ratio was 0.53 (95% confidence interval, 0.32-0.89) favoring TACE treatment.

Transarterial radioembolisation using Yttrium-90 labelled spheres is an alternative to TACE that has become more popular in recent years, though its use is still limited compared with TACE. The efficacy and safety of transarterial radioembolisation appears to be similar to TACE, but there are no randomised trials comparing it with TACE in the literature.

Percutaneous Injection or Radiofrequency Ablation: Percutaneous injection, 95% ethanol, hypertonic saline, NaOH (2N) or acetic acid (50% glacial acid), can be done by direct injection into the tumor. In radiofrequency ablation, a 14-gauge needle directed into the tumor by ultrasound or CT guidance and an alternating current, similar to microwave, is applied. This therapy is best for tumors < 5 cm. There is a complication rate of 2–17% with radiofrequency ablation; complications include bleeding, biliary fistula or stricture, abscess, arteriovenous fistula/aneurysm and needle track seeding. Four-year survival rates ranged from 60% to 80% in well-selected patient populations.

HIFU(High Intensity Focused Ultrasound): High intensity focused ultrasound (HIFU) is a new modality of ablation that is totally non-invasive. Ultrasound focused by a transducer can kill cancer cells by cavitation effect in addition to thermal ablation effect.

Chemotherapy: Chemotherapy is usually given to patients with metastatic, persistent or recurrent disease. Single-agent treatment, such as doxorubicin, platinums, fluoropyrimidines, and gemcitabine, produce an objective response rate of d" 10% without proven survival benefit.Combination chemotherapy can improve the response rate to around 20%, but treatment-related toxicity, mainly myelosuppression, is also much higher.

Targeted Therapy: Sorafenib is a recently developed tyrosine kinase inhibitor (TKI). It inhibits the kinase activity of wild-type B-Raf and mutant Raf, VEGF receptors, PDGFR, c-kit, FLT3 and RET. Sorafenib is antiproliferative and antiangiogenic. The first randomized,

placebo-controlled trial of sorafenib for the treatment of advanced HCC (SHARP trial) was done in Europe and the United States with the primary endpoint of overall survival. The second clinical trial was proposed as a bridging study to evaluate the overall efficacy and safety of sorafenib in the Asia-Pacific population. The treatmentsorafenib 400 mg twice daily-was the same in both trials. Both trials were stopped early because interim analysis indicated significant survival benefit of sorafenib over placebo. The hazard ratios of overall survival and time to progression, respectively, were 0.69 and 0.58 in the SHARP trial and 0.68 and 0.57 in the Asia-Pacific trial.

Sorafenib has been approved for the treatment of advanced HCC by the European Medicines Agency and the US FDA. It is recommended by the US National Comprehensive Cancer Network as a treatment option for HCC patients who are inoperable or who do not present with cancer-related symptoms. A Phase II trial of bevacizumab(10mg/kgevery2weeks)pluserlotinib(150 mg/day) for advanced HCC patients showed a response rate of 28% (14 partial responses out of 57 patients) and a median time to tumor progression of 7.9 months.

Conclusions

The management of HCC has changed dramatically in recent years with improved outcomes. The improved safety and long-term survival after hepatectomy for HCC and the development of minimally invasive liver resection have reinforced the role of liver resection as the first-choice treatment. Local ablative therapies have provided an important alternative for curative treatment for patients who have inadequate liver function reserve for resection. Recurrence after resection or ablation remains a major problem, but active studies are being conducted to evaluate novel adjuvant therapies to improve the prognosis of patients.TACE or radioembolisation is the mainstay of palliation for patients whose HCCs are confined to the liver that is not amenable to resection or ablation. Occasionally, patients with initially unresectable disease can be down-staged to resectable disease after transarterial therapies. Development of novel techniques, such as drug-eluting beads and combination with molecular targeting drugs, may further enhance the efficacy of TACE. Molecular targeted therapy is an important breakthrough that has shown for the first time as a systemic therapy to improve survival of patients with advanced HCC.

(Dr S Veda Padma Priya, DNB Student; Dr Ashish Goel, Consultant, Dept of Surgical Oncology)

GUEST ARTICLE

LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide¹ primarily due to its poor prognosis and high occurrence in cirrhotic livers. One million new cases of HCC are diagnosed every year, resulting in 250,000 to 1 million deaths^{2,3}. Though ablation techniques, especially radiofrequency ablation (RFA) have been proposed as a potential curative therapy for early HCC⁴⁻⁷, resection and liver transplantation (LT) continue to be universally considered the only curative options⁸⁻¹⁰. More patients with HCC and compensated cirrhosis are now being offered the option of resection because of screening and early detection of HCC¹¹⁻¹³, improved patient selection, better perioperative management, and innovations in surgical technique, including the increasing use of laparoscopy^{14,15}. In addition, the possibility of surgical treatment without undue delay (the bane of deceased donor LT - DDLT) and with minimum morbidity and mortality as compared to LT^{11,16-19} are cited as reasons to favour resection over LT.

Unfortunately, most patients do not benefit from hepatic resection for HCC in the long-term because of recurrent disease within the first few years after surgery, the most important cause of death in these patients¹⁹⁻²⁴. After resection, 5-yr overall survival (OS) rates range between 33% and 44%, 5-yr cumulative recurrence rates are 80% to 100%^{11, 16-19}. LT could be considered the optimal treatment for cirrhotic patients with HCC, due to the widest possible resection margins for tumor ("oncological resection") and removal of the underlying cirrhotic liver which is a risk factor for recurrence of HCC and decompensation²⁵⁻³⁰. At least 3 studies have shown that if LT is restricted to patients with early HCC, the risk of recurrence is minimal and survival is similar to that of patients without HCC 31-33. Due to organ shortage, however, the role of LT in HCC patients has been reserved to patients within accepted selection criteria and predominantly to those with altered liver function (late Childs B or C).

The Current Status

In the beginning, LT was a high risk surgery especially with regards to blood loss and perioperative mortality and morbidity. Thus, only non-cirrhotic patients or cirrhotics with relatively well preserved liver function and unresectable HCC were considered good candidates for LT. Also LT for HCC fell into disrepute because livers from deceased donors were scarce in comparison to the number of end stage liver disease (ESLD) patients waiting for them; in addition it was thought unethical to allocate organs to patients not likely to survive long while non HCC, ESLD patients were deprived of a liver.

In 1996, The Milan criteria³¹ (one nodule with a maximal diameter of 5 centimeters or up to 3 nodules with a maximal diameter of 3 centimeters) were first proposed. It was later shown that if these criteria are fulfilled, long term survival following LT for HCC in cirrhotic patients is similar to that following LT for cirrhotic patients without HCC³⁴. These criteria were adopted by the United Network of Organ Sharing (UNOS) as standard criteria for selection of patients with HCC for LT. In the subsequent decade, it became apparent that while these criteria were robust, they were too restrictive and many patients who could do well with LT were being denied the procedure. Yao et al^{35,36} from the University of California, San Francisco Medical Center (UCSF) reported in 2002 that the Milan criteria could be extended to a single tumor up to 6.5 cm, or up to 3 lesions none more than 4.5 cm with a total tumor diameter of up to 8 cm, and similar results could be obtained. Other criteria were later proposed, such as total tumor volume³⁷, the Tokyo criteria³⁸, the Asan Medical Center³⁹ criteria and "Up to seven" criteria; none of these later criteria have been validated in other centers till date (unlike the Milan or UCSF criteria).

The Model for End Stage Liver Disease (MELD) score was designed to ascertain allocation of donor livers "to the sickest patient first" on the DDLT waiting list. Additional MELD points given to patients with HCC within the Milan criteria to prioritize them, has made it possible to decrease dropouts on the waiting list in the DDLT setting with subsequent improvement in long-term disease-free survival (DFS) in these patient⁴⁰. In spite of this, the time on the waiting list for HCC patients is very long due to a limited deceased donor pool, and the dropout rate (due to tumor progression or liver decompensation) is high.

After the first adult-to-adult living donor LT (LDLT) was performed in 1994, the possibility of increasing the donor pool for LT and reducing waiting times on the DDLT list emerged. The safe application of the same criteria

(Milan and UCSF criteria) to select patients for LDLT was supported by some studies⁴¹. In the LDLT scenario, a live related donor donates a portion of the liver to save the life of a loved one. The transplant is not depriving another patient of a life saving organ and there is a possibility of going beyond the accepted criteria for DDLT in HCC patients. The risk to the donor and the utilization of healthcare resources must be weighed against the possibility of curing the patient. Some studies raised questions as to the safety of LDLT as compared to DDLT with regards to oncological outcomes and graft survival in patients with HCC^{42,43}. A recently published intention-to-treat analysis showed that the recurrence and survival outcomes after LDLT and DDLT were comparable with shorter waiting time, preventing dropouts being an additional advantage with LDLT⁴⁴. This study also concluded that LDLT for HCC patients beyond validated criteria (Milan and UCSF) should be proposed with caution.

Our Experience

Though the established criteria (Milan and UCSF) are being largely followed for patient selection for LDLT, several centers have a policy of offering LDLT to patients with no extra-hepatic disease or major vascular invasion⁴⁵⁻⁵⁰, with the contention of offering a survival advantage to the patient without compromising the donor pool in general. At our high volume center (predominantly offering LDLT), we follow anon-restrictive policy towards LDLT for HCC. Presence of extra-hepatic disease, involvement of a major vascular structure by the tumor (including right, left or main portal vein, right, left or middle hepatic vein, inferior vena cava) or medical comorbidity contraindicating transplant, are the only strict contraindications to LT. Size and number of tumors are not considered as exclusion criteria.

Of the 824 LDLTs performed by us from August 2004 to July 2011, the first 417 have completed 2 or more years of follow up. Of these, 70 were done with a diagnosis of HCC based on preoperative imaging and laboratory values and later proved on explant histology. In addition to standard evaluation for LT, patients underwent a full tumor evaluation in the pretransplant period, including a triphasic computed tomographic (CT) scan of the abdomen, radio-isotope bone scan and a whole body PET scan to evaluate for features which could contraindicate LT.

Of the 70 LTs performed for HCC, 11 patients (15.7%) have died till date, giving an OS of 84.3%. Six of these deaths were due to recurrence of tumor whereas

5 deaths were due to other causes (1 chronic rejection, 1 intra-abdominal sepsis, 2 myocardial infarctions and 1 caecal perforation). Two patients are alive at present with recurrence. The 1-year, 3-year and 5-year survival for the entire group was 92.9%, 84.6% and 78.9% respectively.

When we considered our transplanted patients as per standard selection criteria, 28 (40%) were beyond the Milan criteria and 20 (28.6%) were beyond the UCSF criteria. Survival was significantly better in patients within the Milan criteria as compared to beyond (3-yr survival of 91.6% within criteria vs 73.2% outside Milan criteria, p=0.039). Also patients beyond the UCSF criteria had an overall survival of 65% as compared to 91.3% in those within the criteria, and the 1,2 and 3-yr survival were significantly better (p=0.010) for patients within the criteria. The DFS also was significantly better in patients within Milan and UCSF as compared to those beyond. We feel that an overall survival of 71.4% in patients beyond the Milan criteria and a 3-yr survival of 69.6% in patients beyond the UCSF criteria suggests that it is not unreasonable to offer these patients with HCC a LDLT. Without LT, these "beyond criteria" patients are unlikely to survive even for 3-6 months.

Conclusion

LT is by far the best curative option for cirrhotic patients with HCC, both in terms of oncological safety and survival outcomes. Progress in LDLT has opened up anew avenue for increasing the donor pool and achieving long-term outcomes comparable to the DDLT setting. There can be no strict delineating criteria as of now regarding selection of patients with HCC for LDLT. Patients beyond the UCSF criteria are likely to have a higher recurrence rate resulting in a lower but, in the absence of extra-hepatic disease or major vascular invasion, still acceptable survival in the setting of LDLT, as seen from our experience.

While the indication for LT in patients with HCC within conventional criteria is universal, to transplant HCC patients beyond conventional criteria is a centrebased policy, confined largely to high volume LDLT centers since they alone have the data to support its use. Better pretransplant (molecular) prognostic markers than just size and number of tumors are needed before any consensus can emerge on this issue. Until then, as in our center, stringent donor safety measures, an impeccable donor safety record, and low technical failure rate in recipients are essential to justify LDLT for extended criteria HCC.

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GLOBE SCAN

Hepato-biliary Cancers in Germany

Researchers from Germany used incidence and mortality data to determine changes in the frequency of liver disease over the past 30 years. They found that the incidence of and mortality from intrahepatic cholangiocarcinoma (ICC) are rising markedly in Germany. The risk factors underlying this trend are as yet unclear. While overall liver disease mortality has slightly declined in Germany, deaths from hepato-biliary malignancies have declined in women, but remained constant in men. Among hepato-biliary malignancies, ICC stands out, because mortality has more than tripled both in men and women between 1998 and 2008. This is mirrored by a marked increase in new cases reported to local cancer registries, that is, incidence. Over the same time period, HCC and extrahepatic cholangicarcinoma have remained largely constant while gall bladder cancers have declined twofold. The rapid rise in ICC is in line with findings from different regions worldwide, but in contrast to recent data from Denmark and France, two of Germany's direct neighbors.

(Germany: Scand J Gastroenterol, June 22, 2011)

Liver Cancer in Hepatitis C Virus Carriers

A genome-wide study on a group of 3,312 Japanese individuals carrying the hepatitis C virus (HCV), has been conducted by researchers to identify risk factors connecting HCV and hepatocellular carcinoma (HCC). While analysing a total of 467, 538 genetic markers in a group of HCV carriers with and without HCC, the researchers uncovered one single nucleotide polymorphism (SNP) associated with HCC risk, located on a gene called DEPDC5. The significance of the findings was further highlighted when the researchers adjusted their results for gender, age and platelet count, revealing that among Japanese individuals with chronic HCV infection, the DEPDC 5 SNP roughly doubles the odds of developing HCC. The discovery of the DEPDC5 SNP locus provides a valuable target for new therapy techniques, promising progress in the ongoing battle to overcome one of the world's most deadly cancers, which is the third leading cancer related cause of death and the seventh most common form of cancer worldwide.

(Japan: Nature Genetics, July 3, 2011)

PERSPECTIVE

ROLE OF IMAGING IN HEPATO-BILIARY MALIGNANCIES

Introduction

Imaging plays a key role in the diagnosis and staging ofhepato-biliary malignancies. A large number of imaging modalities are available today and a judicious use of these very often helps to characterize a lesion. It is always wise to take into account the clinical parameters and serum marker levels like alpha fetoprotein (AFP) where ever applicable when interpreting imaging studies. Most frequently performed imaging studies are ultrasonography (USG), computed tomograpy (CT) scan, magnetic resonance imaging [MRI (including MRCP)], endoscopic retrograde cholangiopancreaticography (ERCP), positron emission tomography-CT (PET-CT) and sometimes other isotope scans. Image guided biopsies are central to the final diagnosis and are invariably performed by a radiologist. Hepatocellular carcinoma (HCC) is often seen in a cirrhotic liver. Gall bladder (GB) carcinoma is common in the female population in northern India along the Gangetic belt. It is often associated with GB calculi. The highest incidence of GB carcinomais in Chile in Latin America. Imaging features in some of the common hepato-biliary malignancies are mentioned below.

Hepatocellular Carcinoma

Imaging in HCC is a challenge as early diagnosis is critical for successful treatment. Lesions larger than 2 cm usually do not pose a problem. However, nodules smaller than 2 cm often have non-specific imaging features and create difficulties in diagnosis. The sensitivity of MRI and CT for HCC detection is 81% and 68% respectively. Also differentiation of regenerative and dysplastic nodules from HCC, in cirrhosis, is vital for proper management.

USG: Being inexpensive and widely available is frequently used as the initial modality in the work up of focal hepatic lesions. HCC has variable morphological presentations; tumors can be solitary, multifocal or diffusely infiltrating, the most common being a discrete lesion either solitary or multiple. These lesions are usually hypoechoic but are sometimes isoechoic or even hyperechoic (approx 25% cases).

Color Doppler flow imaging is a useful adjunct for detection of vascular invasion. The presence of arterial

waveform within the thrombus indicates that it is neoplastic rather than bland thrombus. This distinction is vital because it has been shown that the presence of malignant portal vein thrombosis has the worst prognosis in predicting recurrence of HCC following surgical resection or liver transplantation.

CT: The advent of helical CT has made it possible to perform multi-phasic examination of the liver in the arterial and portovenous phase with the same bolus of contrast. This includes a non-contrast phase, followed by arterial, venous and delayed phases. On plain CT, most HCCs present as solitary or multiple low attenuation areas. In a fatty liver, HCC may be seen as a hyperdense lesion. Since HCC derives its blood supply from hepatic arteries, on arterial phase the hypervascular tumor shows intense enhancement throughout the tumor. The lesions are frequently encapsulated and the capsule is seen as a hypodense rim. Larger tumors are often heterogeneous due to necrosis and hemorrhage. On portovenous phase, there is rapid washout and the lesion becomes isodense to hypodense to normal liver.

MRI: HCC is hypointense on T1W images and hyperintense on T2W. Fast gradient echo sequences allow the liver to be imaged in a breath hold and dynamic gadolinium enhanced MR imaging has been shown to improve detection of HCC and may be superior to dual phase CT. HCCs enhance intensely on post contrast images, but this feature is not specific as severely dysplastic nodules will also enhance. A more specific feature is washout of tumor below the signal of liver at 2 mins post contrast. The arterial phase also allows distinction from metastatic disease because HCCs typically demonstrate enhancing stroma through the entire tumor whereas metastases have peripheral enhancement.

Angiography: With the advent of dual phase CT and dynamic MRI, angiography is now seldom used for diagnosis of HCC. It is now performed for transarterial chemo-embolization (TACE) to treat the tumor. Classically HCC is seen as a hypervascular mass with tumor angiogenesis, enlarged feeding arteries and early draining veins and a marked tumor blush.

Cholangiocarcinoma

It is a primary tumor arising from the bile duct epithelium and the second most common primary malignant hepatic tumor. There are no specific imaging features that truly distinguish cholangiocarcinoma from HCC or metastases, however, cholangiocarcinoma is more likely to be associated with dilated ducts than HCC or metastases.

OCTOBER 2011

CANCER NEWS

USG: It is the initial screening modality for evaluating biliary dilation. Biliary dilation is the most common indirect sign of cholangiocarcinoma with the abrupt change in ductal diameter indicating the site of the tumor. A definitive mass is rarely seen on USG; thus when the ducts are dilated USG may be helpful in establishing the level of obstruction but an intraductal or infiltrating lesion causing the obstruction may be difficult to visualize. Peripheral cholangiocarcinomas may appear as a solitary mass or as diffusely abnormal echotexture. Because of their non-specific symptomatology, mass forming lesions are far advanced when detected at USG.

CT: The CT appearance varies depending on the anatomic location of the lesion relative to the biliary tract. After administration of contrast agent, most cholangio-carcinomas remain hypoattenuating during arterial and venous phases and show enhancement during delayed phase, findings that reflect their hypovascular desmoplastic composition. In recent years, several studies involving CT cholangiography with IV contrast agents have shown promising results in the non-invasive visualization of biliary tree. However, it is dependant on the secretory function of the biliary system; the use of this modality might be limited in patients with high grade obstruction or significantly elevated bilirubin levels.

MRI: MR imaging with MR cholangiography and dynamic contrast enhanced MR angiography is yet another modality for the comprehensive evaluation of cholangiocarcinomas. They typically appear isointense to hypointense on T1W and hyperintense on T2W images. Minimal or incomplete enhancement is seen at the periphery on early images, whereas delayed progressive enhancement is seen on late phase images. Although MR cholangiography offers all the benefits of a non-invasive tool in the evaluation of the biliary tree and is now an established alternative to ERCP, reliable differentiation of a malignant from a benign stricture is not always possible at MR imaging. Therefore, some patients still require ERCP for bile sampling and cytologic analysis to establish a diagnosis and for relieving biliary obstruction with biliary stent placement.

Gall Bladder Cancer

GB cancer is the fifth most common malignancy of the gastointestinal tract and is found incidentally in 1-3% of cholecystectomy specimens. Early diagnosis of GB cancer is difficult because most patients present with non-specific findings and by the time of diagnosis, most patients



GB Mass (closed arrows) with Calculi (open arrows) are considered unresectable. This neoplasm has three patterns of presentation.

Focal or diffuse mural thickening: This is the least common presentation and the most difficult to diagnose. Although CT is inferior to USG in depicting mucosal irregularity, mural thickening and cholelithiasis, it is superior for evaluating the thickness of portions of the GB wall that are obscured by gall stones or mural calcification on USG.

An intraluminal polypoid mass: Approximately 25% of GB cancers present as intraluminal masses. Small polypoid carcinomas can be difficult to differentiate from a cholesterol polyp, adenoma or adherent stone. On CT & MR, these cancers enhance homogeneously after contrast administration and usually lack calcification or necrosis.

Subhepatic mass replacing the GB: This is the most common presentation and presents as a solid mass with variable echogenicity. Infiltrating carcinomas that replace the gall bladder often show irregular contrast enhancement with scattered regions of internal necrosis on CT &MR. **PET-CT**

FDG PET is more useful in detecting metastases to liver, lymph nodes or other distant sites. It is useful in staging and restaging of all hepato-biliary malignancies.

Conclusion

Imaging in hepato-biliary malignancies has matured with the advent of modern imaging techniques like triple phase CT and MRCP. It is possible to diagnose HCC and GB malignancy with a fair degree of accuracy. These advances in imaging are helping the clinician in quick decision making and offering timely treatment strategies to the patients.

(Dr Arvind K Chaturvedi, Director; Dr Mani Jain, Resident, Dept of Radiology)

IN FOCUS

SYSTEMIC THERAPY OF GALL BLADDER CANCER

Introduction

Gall bladder cancer is a common cancer in North West India, where the incidence is approximately 7.4 per 100000 with a 6:1 female to male ratio. Less than 15% of gall bladder cancers (GBC) are amenable to upfront or curative surgical extirpation. Majority of these cancers present in a loco-regionally advanced stage, involving neighboring and distant liver segments & regional/ distant lymph nodes or causing obstructive jaundice in 35-55% of patients and/or gastric outlet obstruction in 20%. Right hypochondrial pain occurs in over 50% of patients. The systemic management involves: (i) control of malignant process, (ii) amelioration of hepatic dysfunction/or ascites, (iii) control of fluid and electrolyte balance, and (iv) control of pain & intestinal obstruction.

Chemotherapy

Chemotherapy is used in the management of GBC in several settings: (i) adjuvant following surgical resection, usually with radiation; (ii) for locally advanced unresectable disease, either alone or in combination with radiation; and (iii) for patients with metastatic disease.

PEFG regimen (Cisplatin, Epirubicin, 5-FU, Gemcitabine) was given in 37 patients with 'biliary tract cancer' (BTC). A partial response was obtained in 16 patients (43%) and stable disease in 12 (32%). The median overall survival (OS) was 12.1 months and 1 year OS was 52%. The median progression-free survival (PFS) was 7.9 months & the six month-PFS was 67%.

Infusional 5-FU plus cisplatin: Infusional 5-FU has been combined with cisplatin in at least two trials. In one trial, 5-FU(1 gm/m² by continuous infusion daily for five days) plus cisplatin (100 mg/m² on day 2) resulted in partial remission in six patients (24%); one was a longterm survivor after receiving additional local therapy. Median OS for patients with GBC was 11.5 months.

Leucovorin-modulated 5-FU: Leucovorin-modulated 5-FU has a favorable toxicity profile but only modest antitumor activity. In one report of 28 patients with advanced BTC, 5-FU (375 mg/m² per day by bolus) followed by leucovorin (25 mg/m² per day) was given on days 1 through 5, every three to four weeks. The overall

objective response rate (ORR) was 32%, with two complete responses.

Capecitabine with and without oxaliplatin: Capecitabine, an orally active fluoropyrimidine derivative, appears to be an active agent for GBC, both as a single agent and in combination with cisplatin and oxaliplatin. In a report of 63 patients with hepato-biliary malignancies, which included 8 with GBC, capecitabine (2000 mg/m² daily for 14 of every 21 days) produced an objective response in 4 (50%) of the patients with GBC, 2 of which showed complete response. In contrast, there were no responses among those with cholangio carcinoma. In another trial, capecitabine (1000 mg/m² twice daily on days 1 to 14) plus oxaliplatin $(130 \text{ mg/m}^2 \text{ over one hour on day } 1)$ were administered to 65 patients. Of the 27 patients with GBC, there was 1 complete and 7 partial responses; an additional 9 had stable disease (total disease control rate 63%). The median OS was 11.3 months.

Gemcitabine and gemcitabine based combinations: Gemcitabine is an active agent, both as monotherapy and in combination regimens. Reported clinical benefit rates (partial response plus stable disease) with single agent gemcitabine (1000 to 1200 mg/m² weekly for three of every four weeks) are in the range of 15 to 60% (with ORR between 11 and 53%). In most studies, median OS is 11 months or less, although three Phase II trials report median OS durations of 13 to 16 months with the combination of gemcitabine plus capecitabine.

Gemcitabine plus 5-FU and leucovorin: In a Phase II multicenter trial involving 40 patients with BTCs (22 with GBC), gemcitabine (1000 mg/m² weekly for three of every five weeks) was given alone (n=18) or gemcitabine (1000 mg/m² days 1 and 8, every 21 days) was given with 5-FU (400 mg/m² bolus followed by 22hourinfusion of 600 mg/m², every 21 days) and leucovorin (100 mg/m² over two hours day 1, every 21 days), (n=22). Partial responses were noted in 22 and 36% of patients receiving gemcitabine alone or with 5-FU and leucovorin, respectively, and the median time to progression was 3.4 and 4.1 months. A second multicenter Phase II trial of gemcitabine/5-FU/leucovorin reported three partial responses among 14 cases of GBC (ORR 21%), and the median time to progression and OS were 5.2 and 7.2 months, respectively.

Gemcitabine plus capecitabine: The combination of gemcitabine and the oral 5-FU prodrug, Capecitabine seems to be associated with higher response rates than gemcitabine plus 5-FU for advanced BTC, and at least

three Phase II trials reported a median survival of 13 to 16 months. A study of 75 patients showed 22 objective responses (3 complete), which were seen in both tumor types. The median PFS and OS rates were 6.2 and 12.7 months, respectively. The Southwest Oncology Group (SWOG) studied gemcitabine (1000 mg/m² over 100 minutes on days 1 and 8) plus capecitabine (650 mg/m^2) twice daily for 14 of every 21 days) in 57 patients with unresectable or metastatic GBC (n=17) or cholangiocarcinoma (n=35). Nine patients had partial responses (response rate 18%), and 14 (27%) had stable disease. Only four patients developed grade 4 neutropenia. Median OS was 7 months. In a second study of combined therapy in 45 patients, 22 with GBC, the median OS duration was 14 months (19 months for cholangiocarcinoma and only 6.6 months for GBC).

Gemcitabine plus cisplatin: Combined gemcitabine plus cisplatin is also an active regimen. The superiority of gemcitabine plus cisplatin over gemcitabine alone was shown in the multicenter ABC-02 trial, in which 410 patients with locally advanced (25%) or metastatic bile duct (n=242), gall bladder (n = 148) or ampullary (n=20) cancer were randomly assigned to six courses of cisplatin (25 mg/m²) followed by gemcitabine (1000 mg/ m²) on days 1 and 8, every 21 days, or gemcitabine alone (1000 mg/m² days 1, 8, 15, every 28 days). At a median follow-up of 8.2 months, median OS was significantly greater with combination therapy (11.7 versus 8.1 months), as was median PFS (8 versus 5 months). Toxicity was comparable in both. Gemcitabine plus cisplatin should be considered the reference regimen for advanced biliary cancer. However, gemcitabine/cisplatin combination has not been directly compared to other gemcitabine combinations (eg, with capecitabine, leucovorin-modulated 5-FU, or oxaliplatin) or capecitabine plus oxaliplatin in randomized trials.

A pooled analysis of 104 trials of a variety of chemotherapy regimens in advanced BTC concluded that gemcitabine/ cisplatin should be considered a standard option for advanced GBC, but not the definitive reference standard. The substitution of carboplatin reduces the severity of nonhematologic toxicity, but myelosuppression is sometimes worse.

Gemcitabine plus oxaliplatin: Some studies have reported antitumor efficacy and good tolerability for GEMOX (gemcitabine plus oxaliplatin). In a Phase II study, the response rate was 36%, and median OS duration was 14.3 months using every other week

gemcitabine (1000 mg/m² day 1) and oxaliplatin (100 mg/m² day 2) in a select group of 31 previously untreated patients with advanced BTC (19 with GBC), a good performance status, and a serum bilirubin level <2.5 times the upper limit of normal. Results were less favorable in the 25 other patients with poorer performance status, receiving second or third line therapy, or with a higher bilirubin level (response rate 22%, median survival 7.6 months). Other studies have reported a far lower ORR with this regimen in advanced GBC (1 of 23 patients, 4%) as compared to non-gall bladder BTCs (9 of 44, 21%).

Gemcitabine plus oxaliplatin and 5-*FU:* A Phase II trial of 37 patients with advanced GBC using gemcitabine + oxaliplatin and aweekly infusion of 5-FU seems promising. Gemcitabine (900 mg/m²) was followed by oxaliplatin (65 mg/m²)+5-FU (1500 mg/m² over 24 hr), all drugs on days 1 and 8 every three weeks; 8 had a partial response; nonhematologic toxicity was low, and the median OS was 10 months, with 34% of patients still alive at one year.

Docetaxel: Activity of docetaxel (100 mg/m² every 21 days) was shown in a trial of 25 patients with unresectable or metastatic BTC (ORR 20%); grade 3 or 4 neutropenia occurred in 56%.

Targeted Therapy

In one study, 42 patients with advanced BTC received erlotinib (150 mg/d). There were three partial responses (2 with documented expression of EGFR) and a PFS of 16%. Lapatinib was evaluated in 17 patients, 5 had stable disease. Combination therapy with bevacizum abander lotinib was studied in 34 patients, 7 had stable disease. Sunitinib, sorafenib and gefit in bhave 20-30% single agent response rates, and median survival times from 2.3 to 3.7 months.

Recommendations

For initial therapy in patients with a good performance status, gemcitabine plus cisplatin (Grade 2B) or gemcitabine plus capecitabine (Grade 2C) is suggested. For patients with a borderline performance status, gemcitabine as a single agent (Grade 2C) is suggested. Supportive care alone is also an appropriate alternative.

No regimen can be considered standard after failure of an initial gemcitabine-based regimen. However, an oxaliplatin-based regimen, such as capecitabine plus oxaliplatin or oxaliplatin plus short-term infusional 5-FU and leucovorin (Grade 2C), can be considered in patients with good performance status.

(Dr (Col) Prakash G Chitalkar, Ex Sr Consultant; Dr Rajeeb Deo, Sr Resident, Dept of Medical Oncology)

RESEARCH & DEVELOPMENT

Antiviral Therapy after Hepatectomy

Retrospective analysis of a prospectively collected database showed that commencement of antiviral therapy after hepatectomy, especially in early-stage tumors, improves the prognosis of hepatocellular carcinoma (HCC) in preoperatively antiviral-naïve patients with chronic hepatitis B virus (HBV) infection. Among 135 patients who underwent major hepatectomy for HBVrelated HCC, 42 patients received antiviral therapy (treatment group) after hepatectomy, whereas 94 did not (control group). The 1-, 3- and 5-year overall survival rates in the treatment group were 88.1%, 79.1% and 71.2%, and 76.5%, 47.5% and 43.5% respectively in the control group. The 1-, 3-, and 5-year disease-free survival rates in the treatment group were 66.5%, 51.4% and 51.4% and in the control group the rates were 48.9%, 33.8%, and 33.8% respectively. Subgroup analysis stratified against tumor stage and major vascular invasion showed that post-hepatectomy antiviral treatment conferred a significant survival benefit in stages I and II tumors or HCCs without major venous invasion.

(Arch Surg, June 2011)

Assessment of Response to Chemoembolization

Phosphorus-31 MR spectroscopy is a promising technique for the noninvasive assessment of hepatocellular carcinoma (HCC) response to chemoembolization. Researchers evaluated 17 HCC target tumors with (31)P MR spectroscopy before and after chemoembolization. Of the 17 lesions evaluated, 12 lesions were responsive to chemoembolization, whereas 5 were not. In the responsive group, the phosphodiesters (PDE)/total phosphorus content (TPC) ratio was significantly decreased after chemoembolization, whereas the nucleoside triphosphates (NTP)/TPC ratio was significantly increased. In the non-responsive group, phosphorus metabolism had no significant changes after treatment. Threshold percentage change of the PDE/ NTP value was 1.25% with 91.7% sensitivity and 100% specificity for identifying tumor response to chemoembolization and the threshold percentage change of the NTP/TPC value was 15.3% with 75% sensitivity and 100% specificity. Further studies are necessary to confirm these preliminary results.

(J Vasc Interv Radiol, June 22, 2011)

Predictive Marker for Recurrence of HCC

Keratin (K)19 positivity has been reported to be a useful predictive marker for recurrence in patients with hepatocellular carcinoma (HCC) who have undergone hepatic resection. Researchers from Japan investigated that expression of Keratin 19 is related to high recurrency of HCC after curative radiofrequency ablation (RFA). They retrospectively evaluated the clinicopathological features, including imaging and K19 expression in 246 patients with HCC who were within the Milan criteria and had received curative RFA. Using a two-step insertion method, tumor biopsies were obtained just prior to RFA and were evaluated histologically. Tumor seeding due to liver biopsy and RFA was not observed. Ten patients had K19-positive HCC. Imaging findings were similar between K19-positive and K19-negative HCC. Nine out of 10 patients who had K19-positive HCC had recurrence of HCC after RFA, and intrahepatic recurrences were observed within 12 months in 6 out of 10. According to this study, K19 positivity was a significant risk factor for recurrence and early recurrence (<1 year after RFA). K19 expression was an independent risk factor for tumor status exceeding the Milan criteria after RFA.

(Oncology, July 7, 2011)

Role of Metabolic Syndrome in Liver Cancer

Metabolic syndrome comprises a group of medical conditions which include central obesity, raised fasting glucose levels and diabetes mellitus, raised triglycerides, reduced HDL cholesterol and hypertension. While metabolic syndrome is a recognized risk factor for HCC and may also modify intrahepatic cholangiocarcinoma (ICC) risk, the magnitude of this effect has not been investigated on a large scale in the US. The researchers examined the association between metabolic syndrome and development of primary liver cancers in the general US population. Their findings showed a 2-fold increased risk of HCC and a 1.56-fold increased risk for ICC in individuals with preexisting metabolic syndrome. The risk of developing these primary liver cancers is significant for individuals with this condition. Due to high prevalence of metabolic syndrome, even small increase in the absolute risk of HCC and ICC may contribute to the increasing liver cancer burden. Thus, metabolic syndrome may be the source behind a number of the idiopathic HCC or ICC cases in the US and efforts to control the worldwide epidemics of obesity and diabetes could reduce the liver cancer burden.

(Medical News Today, July 21, 2011)

NEW TECHNOLOGIES

DIAGNOSTICS

Miniaturized Device for Diagnosing Cancer

The miniaturized nuclear magnetic resonance, or micro-NMR device, can diagnose cancer within an hour, using patient samples of just a few thousand cells that are collected using a fine needle and a syringe. The device detects magnetic nanoparticles attached to antibodies, which flag protein biomarkers known to be associated with some cancers in patient samples. The physician can operate the portable device, roughly the size of a cube-shaped box, from the patient's bedside with a smart-phone application that displays results on the phone's screen. Using a four protein signature, researchers at Massachusetts General Hospital were able to diagnose a range of epithelial cancers, including lung, breast pancreatic and gastrointestinal, with 96% accuracy. The initial clinical studies indicate that the micro-NMR system may be more accurate than standard diagnostic techniques.

(Cancerbulletin, March 22, 2011)

Plasma Circulating DNA for Detection of HCC

Plasmacirculating DNA may be a potential biomarker for diagnosis and prognosis of hepatocellular carcinoma (HCC). In a study, the researchers collected blood samples from the patients with HCC, liver cirrhosis or chronic hepatitis, and the control group. Plasma DNA was extracted and quantified by a real-time quantitative PCR method. DNA levels in the HCC plasma were significantly higher than those in the healthy controls or control benign patients (P<0.001). Plasma DNA detection could discriminate HCC from normal controls with 90.2% sensitivity and 90.3% specificity in receiver-operation characteristic (ROC) analysis. Combined ROC analyses using plasma DNA and serum AFP revealed an elevated AUC of 0.974 with 95.1% sensitivity and 94.4% specificity in discriminating HCC from normal controls. The plasma DNA levels were positively associated with tumorsize, and were significantly elevated in HCC patients with intrahepatic spreading or vascular invasion. The overall survival time of patients with high plasma DNA levels showed a shortened trend as compared with patients with low plasma DNA concentrations.

(Pathol Oncol Res, Jul 21, 2011)

DRUGS

Bavituximab

Bavituximab is a first-in-class phosphatidylserine (PS)-targeting monoclonal antibody that represents a new approach to treating cancer. PS is a highly immunosuppressive molecule usually located inside the membrane of healthy cells, but "flips" and becomes exposed on the outside of cells that line tumor blood vessels, creating a specific target for anti-cancer treatments. PS-targeting antibodies target and bind to PS and block this immunosuppressive signal, thereby enabling the immune system to recognize and fight the tumor. Study conducted by Peregrine Pharmaceuticals, Inc showed that bavituximab significantly enhanced the anti-tumor effects of sorafenib in models of hepatocellular carcinoma (HCC), with 69% less growth compared to sorafenib alone. The data suggests that the growthblocking mechanisms of sorafenib combined with the vascular-targeting and immune-reactivation mechanisms of bavituximab may offer additive anti-tumor effects for patients with HCC. An ongoing Phase I/II trial is evaluating bavituximab with sorafenibin patients with advanced HCC.

(Peregrine Pharmaceuticals, April 5, 2011)

Selumetinib for Biliary Cancers

Biliary Cancers (BCs) carry a poor prognosis, but targeting the RAS/RAF/mitogen-activated protein kinase (MEK)/extracellular signal related kinase (ERK) pathway is of significance. Selumetinib, also known as AZD6244 (ARRY-142886), blocks MEK, which cancer cells need to proliferate and survive. A multi-institutional Phase II trial of selumetinib in patients with metastatic biliary cancers has shown promising results. The study provides a strong rationale for developing this agent further in larger trials, probably in combination with other drugs, which would enable to establish a new standard of care for biliary cancers in the near future. Selumetinib belongs to a class of drugs, called protein-kinase inhibitors. This agent selectively inhibits the protein kinase MEK1 and MEK2. It is part of a signaling pathway that is often damaged in biliary cancer cells. Patients who lacked a target protein called pERK did not seem to respond to the drug, suggesting that the drug may not work if the protein is missing in the cancer cells. This finding suggests that in the future, we may be able to identify which patients are most likely to respond to the drug.

(JCO, June 10, 2011)

TECHNIQUES

Intraoperative Ultrasound for Liver Carcinoma

Contrast-enhanced intraoperative ulatrasound (CE-IOUS) using sonazoid (gaseous perflubutane), a novel ultrasonic contrast agent enabling Kupffer imaging, may enable differentiation of hepatocellular carcinoma (HCC) among new focal liver lesions found during fundamental intraoperative ultrasound (fundamental-NFLLs). Fundamental-NFLLs and CE-IOUS were performed successively in 192 patients after laparotomy. A tentative diagnosis of HCC was made when a lesion was either hypervascular during the vascular phase or hypoechoic during the Kupffer phase. A final diagnosis of HCC was made on the basis of the results of a histological examination or dynamic computed tomography findings obtained during the 12-month post-operative period. Seventy-nine fundamental-NFLLs were found in 50 patients, 17 of which were finally diagnosed as HCC. The sensitivity, specificity, and accuracy of CE-IOUS for differentiating HCC among fundamental-NFLLs were 65%, 94% and 87%, respectively. CE-IOUS identified 21 additional new hypoechoic lesions in 16 patients, of which 14 lesions in 11 patients were finally diagnosed as HCC. With the help of CE-IOUS using sonazoid, more accurate intraoperative staging for HCC can be performed.

(Ann Surg, June 20, 2011)

New Technology for Liver Transection

Liver precoagulation with microwave technology is a novel and efficient technique with minimal morbidity and mortality for liver transection. Under this technique, Glisson's capsule was incised after securing inflow and outflow control. Two antennae, 2 cm apart, connected to a 915-MHz generator, were inserted 5 cm into liver parenchyma at a 130° angle. Once the parenchyma was firm and changed its colour to gray, the antennae were advanced along the line of transection. The parenchyma was divided with electrocautery. In a series of 35 patients undergoing liver resections, median operative time for major resection was 188 and 251 minutes for minor resection. There was no post-operative mortality. Bile leak needing stenting occurred in one patient. Intraoperative transfusion was required in nine major and one minor resection. Other complications were ileus in four, deep vein thrombosis in two, intra-abdominal abcess in one and cardiac events in two patients.

Novel Cell Separation Strategy

To establish a sensitive and specific isolation and enumeration system for circulating tumor cells (CTC) in patients with hepatocellular carcinoma (HCC), the researchers from China used a novel cell separation strategy. HCC cells were bound by biotinylated asial of etuin and subsequently magnetically labeled by antibiotin antibody-coated magnetic beads, followed by magnetic separation. Isolated HCC cells were identified by immunofluorescence staining. The system was used to detect CTCs in 5 ml blood. Blood samples spiked with Hep3B cells were used to determine recovery and sensitivity. Prevalence of CTC was examined. CTC samples were also analysed by FISH. The average recovery was 61% or more at each spiking level. CTCs were identified in 81% HCC patients. Both the positivity rate and the number of CTCs were significantly correlated with tumor size, portal vein tumor thrombus, differentiation, status and tumor-node-metastasis classification and the Milan criteria. HER-2 gene amplification and TP53 gene deletion were detected in CTCs. The system provides a new tool allowing for highly sensitive and specific detection and genetic analysis of CTCs in HCC patients. It is likely clinically useful in diagnosis and monitoring of HCC and may have a role in clinical decision making.

(Clinical Cancer Research, June 1, 2011)

Shrinking Liver Tumors

A potential new option is beginning to emerge for patients with hepatocellular carcinoma (HCC), that often does not respond well to chemotherapy. Researchers administered very low levels of an electromagnetic field, emitting from a spoon-like device placed in the patient's mouth, to 41 patients with HCC. After six months, the tumor in 14 patients had stabilized after each received three onehour treatments per day each day. The very appealing advantage of this novel therapy is its capability to shrink tumors without collateral damage. With this treatment, seven of the eleven patients who reported pain prior to the start of their treatment reported either a complete disappearance of pain or decrease in degree. Preliminary evidence also indicates that the treatment not only affected the primary cancer, but also its metastases. When the device is put in the mouth, the whole body receives a tiny but fairly homogeneous amount of radiofrequency. The researchers believe it to be a promising therapy that could become a standard of care in the near future.

(Am Surg, Apr 2011) (7

(The UAB Comprehensive Cancer Center, Aug 9, 2011)

CLINICAL TRIALS

Adjuvant Treatment for Ampullary Cancer

The largest randomized ampullary cancer ESPAC-3 (V2) trial examined the survival effect of adjuvant chemotherapy against observation after resection and within the chemotherapy group to compare 5-fluorouracil/ folinic acid (5-FU/FA) versus gemcitabine. Among 304 patients enrolled, median overall survival (OS) for chemotherapy (57.1 months) versus no chemotherapy (43.0 months) gave an HR of 0.85. For R0 patients, median OS for chemotherapy (58.4 months) versus no chemotherapy (45.1 months) gave an HR of 0.78. There was a survival outcome benefit from chemotherapy in the subset of patients with R0 resection using multiple regression with an HR of 0.73. Regarding the type of chemotherapy administered, no significant survival differences were noted with gemcitabine compared to 5-FU/FA, although gemcitabine was better tolerated. The trial suggests a benefit for adjuvant monochemotherapy in patients with clear resection margins.

(Journal of the Pancreas, July 2011)

Regimen for Palliative Chemotherapy

Researchers have conducted a multicenter. randomized Phase III trial to compare between gemcitabine/oxlaplatin (GEMOX) versus GEMOX plus erlotinib (Tarceva[T]) (GEMOX/T) as first-line chemotherapy in unresectable, metastatic histopathologically confirmed adenocarcinoma of biliary tract (CCC), ampula of vater (AOV) or gall bladder (GB). 268 patients were randomized, 133 patients to GEMOX arm and 135 patients to GEMOX/T arm. With a median follow-up of 13.9 months, median PFS was 5.8 months in GEMOX/Tarm and 4.2 months in GEMOX arm. In subgroup analysis (CCC, n=180), however, median PFS was significantly longer in GEMOX/T arm (5.9 months) when compared with GEMOX arm (3.0 months). The overall response rate was significantly higher in the GEMOX/T arm when compared with GEMOX arm. There was no significant difference in overall survival between the two arms. Although PFS was not prolonged in GEMOX/T, there was a significant benefit in terms of PFS in GEMOX/T arm for CCC patients.

(JCO, June 20 Suppl, 2011)

Targeted Therapy in Liver Cancer

Nexavar® (sorafenib) provides superior overall survival to Sutent® (sunitinib) in the treatment of hepatocellular cancer (HCC). These results were presented at the 2011 annual American Society of Clinical Oncology meeting. Nexavar® is approved for the treatment of HCC that is not able to be surgically removed. Sutent® is approved for the treatment of gastrointestinal stromal tumors and for advanced renal cell cancers. Researchers from Asia conducted a Phase III clinical trial directly comparing treatment with Nexavar® and Sutent® in HCC. The trial included patients with advanced cancer who had not received prior chemotherapy. Overall survival was greater in the group treated with Nexavar® (10 months) compared with the group treated with Sutent® (8.1 months). Progression-free survival and time to cancer progression were similar between the two treatment groups. Side effects were greater among the group treated with Sutent®, leading an independent data monitoring committee to stop the trial early based on safety issues. These results indicate that Nexavar® provides superior survival results compared with Sutent[®] in the treatment of advanced HCC. Furthermore, the side effects associated with Sutent® resulted in the trial closing earlier than planned.

(New Mexico Cancer Center, June 23, 2011)

Treatment of Advanced Hepatocellular Carcinoma

With the aim to investigate more effective and safe systemic treatment options for patients with advanced hepatocellular carcinoma (HCC), a Phase II study was designed to determine the efficacy and toxicity of the combination of bevacizumab, capecitabine, and oxaliplatin in patients with advanced unresectable and untransplantable HCC. Forty patients were enrolled in the study. Forty percent had an Eastern Cooperative Oncology Group performance status (PS) of 0, 55% had PS of 1 and 5% had PS of 2. Forty percent of patients had hepatitis B virus infection. The median progression-free survival was 6.8 months and the median overall survival was 9.8 months. Eight patients achieved partial response; 23 patients had stable disease with overall 77.5% disease control rate. The combination was tolerable with limited grade 3/4 toxicity, mainly peripheral neurotoxicity and fatigue. Thus, the combination appeared effective and safe, and the results were encouraging leading to the consideration of further investigation.

(Cancer, July 15, 2011)

THYROCON-2011

Preamble

THYROCON-2011 organised by the Rajiv Gandhi Cancer Institute & Research Centre (RGCI&RC), Delhi focused on Recent Advances and Controversies in Thyroid Cancer. The CME & the Live Surgical Workshop held on the 20th-21st August 2011, was conducted under the aegis of the Foundation for Head & Neck Oncology, India, Association of Surgeons of India (ASI, Delhi Chapter) and the Association of Nuclear Medicine Physicians of India. Attended by 250 delegates from all over the country, THYROCON-2011 was a big success and added a feather in the cap of the organizational skills of RGCI&RC.

The CME commenced with a welcome address by Dr AK Dewan, Medical Director of RGCI&RC. This was later followed by an introduction to the conference by Dr PS Choudhary, the organizing secretary & Director Nuclear Medicine, RGCI&RC.

Live Surgical Workshop

The live operative session, the main attraction of any CME, were performed with great élan and dexterity. Dr Anil D'Cruz, Director Tata Memorial Hospital (TMH), Mumbai and Dr Ravi Deo, Senior Consultant, Manipal Hospital, Bangalore, shared the finer nuances of a good thyroidectomy and neck dissection. The message was forthrightly put across to the youngsters, with regards to tissue respect and the importance of preserving the parathyroids. The sessions were ably moderated by a team of varied surgeons from various prime institutions of India. Towards the culmination of the operative session, Dr Ashok R Shaha, the invited international faculty from Memorial Sloan Kettering Cancer Centre (MSKCC), New York, enthralled the audience, sharing his views pertaining to different controversial issues in management of thyroid cancer.

Scientific Sessions - Day 1

Following a stimulating tea break, the first theoretical scientific session focused on varied basic issues. A sound anatomical knowledge is indeed the backbone of a good and meticulous surgeon; reiterating this fact was Dr TK Thusoo, Director General and Endocrine Surgeon, Max Hospital, New Delhi. The presentation titled as "Anatomical trifles of thyroid gland' highlighted the different anomalies which could throw surprises on the operating field.

Dr Kavita Sahai, Senior Advisor, Base Hospital, Delhi Cantt and Col Reena Bhardwaj, Senior Advisor in Pathology and Oncopathology, Army Hospital (R&R), Delhi Cantt, discussed about the pitfalls and molecular and genetic alterations in thyroid cancer respectively. Microscopic classification and subtle difference between solid variant of Papilliary Thyroid Cancer (PTC) and poorly differentiated carcinoma was highlighted. The BRAF mutation in PTC had a great bearing on its aggressiveness, manifesting clinically with a more advanced presentation.

Dr S Avinash Rao, Senior Consultant, Radio Diagnosis, RGCI&RC, spoke about the role of conventional imaging in thyroid cancer. The role of Ultrasound and Color doppler in the staging of the tumor, follow up and differentiation of benign from malignant diseases was elaborated upon. The distinct role of Computed Tomography, Magenetic Resonance Imaging and Scintigraphy in surgical planning was discussed.

Dr Choudhary highlighted the role of the various pharmaceuticals, such as ¹⁸F-FDG, ¹⁸FDOPA, ⁶⁸Ga– labeled pharmaceutical and ¹²⁴IPET. Through evidence from literature, it was shown that a positive PET scan with greater number of PET avid lesions and a higher SUV distinctly showed an egative impact on the prognosis of the patient.

The next session was completely devoted to the various optimum treatment strategies to be adopted for thyroid malignancies. The opening presentation of this session by Dr Shaha was thoroughly detailed, supported with level I evidences from landmark articles. Optimization of treatment modalities for low, intermediate and high-risk patients was highlighted. At the end of the deliberations, the basic message conveyed through the presentation was that a 'good judgement comes from experience and experience comes from bad judgement'.

"Optimal strategy for lymph node dissection" by Dr SK Mishra, Head, Endocrine Surgery, SGPIMS, Lucknow, detailed the indications for central compartment lymph node dissection (CCLND) in patients with clinically involved central compartment nodes and prophylactic CCLND for T3 and T4 well differentiated thyroid carcinoma with clinically uninvolved central nodes. Fraught with complications of hypo-parathyroidism and recurrent laryngeal nerve injury, the indications of CCLND were clearly reinstated. He emphasized on the

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need of comprehensive neck dissection in proven neck node metastasis.

Dr R Michael Tuttle, Prof of Endocrinology & Nuclear Medicine, MSKCC, discussed in detail and summarised the entire concept of utility of adjuvant radio-iodine therapy in thyroid malignancies. He also enumerated the role of recombinant thyroid stimulating hormone (rTSH) in thyroid ablation and metastatic diseases.

The panel discussion moderated by Dr Ashok R Shaha, on Well Differentiated Thyroid Cancer, was an extremely well conducted discussion, with a healthy rebuttal from an intelligible set of panelists. The concluding session of the day, touched upon diverse issues pertaining to thyroid cancers, such as the role of rTSH, pediatric thyroid malignancies, incidentalomas and management of retrosternal goiters.

The evening saw ceremonial welcome of the delegates and the various faculty members. The occasion was graced by Prof Dilip Bandyopadhyay, Vice Chancellor of the Guru Gobind Singh Indraprastha University.

Scientific Sessions - Day 2

The day 2 of the CME started on an extremely pleasant note with tete-a-tete with the learned and erudite professors in 'Meet the Professors'. Even this morning session witnessed a hall filled to capacity.

Dr Chandrasekarn, Head of Endocrine Surgery, Madras Medical College, highlighted the management strategies for medullary thyroid carcinoma. Whether locally invasive thyroid cancers mandate an aggressive approach, was lucidly depicted by Dr Dewan. Issues pertaining to complications in thyroid surgery and the clinical acumen required to prevent them were well touched upon by Dr Shaha. The interesting part of the session was practicing thyroidectomies in a rural setting, using simple cervical nerve blocks. Sharing his experience was Dr Madan Kapre, a senior ENT consultant from Nagpur.

Role and evidence of External Beam Radio Therapy in thyroid malignancies, a controversial issue, was detailed by Dr J P Aggarwal, Additional Prof, Dept of Radiation Oncology, TMH, Mumbai. (Col) R Ranga Rao, Director-Medical Oncology, BL Kapur Memorial Hospital, New Delhi, highlighted the role and implication of targeted therapy in thyroid cancer.

Panel discussion on Medullary and Poorly Differentiated Thyroid Cancers was brilliantly conducted



(Left to Right: Dr PS Choudhury, Director, Nuclear Medicine; Dr Tapaswini P Sharma, Consultant, Surgical Oncology; Mr DS Negi, CEO; Prof Dilip K Bandopadhyay, Hon'ble Vice Chancellor, Guru Gobind Singh Indraprastha Univerisy, Delhi; Mr Rakesh Chopra, Chairman; Dr AK Dewan, Medical Director & Sr Consultant, Surgical Oncology)

by Dr D'Cruz. The case capsules had been well formulated and provoked a lot of active participation from the audience.

The concluding scientific session dwelt upon issues pertaining to parathyroid carcinoma which were discussed in depth by Dr Chintamani. Nerve monitoring and its role in thyroid surgery was analysed with critical comments on the use of monitors. Great emphasis on a sound anatomical knowledge of the nerve was reiterated through presentation by Dr Jyoti Dabholkar, Head of the ENT Department, KEM, Mumbai. Dr KS Gopinath, Head, Surgical Oncology discussed in simple terms the differences in the ETA and the ATA guidelines. The session concluded on a cheerful note with a presentation on Robotic thyroidectomy by Dr Tapaswini P Sharma, followed by video presentation of the same by Dr Ashish Goel, Consultant, Head & Neck Surgery, RGCI&RC.

At the end of the day, it was an extremely gratifying experience for the organizers for having done justice to all the delegates from India and abroad. The scientific content was well applauded. For years to come, this institution would graciously grow with an academic temper and nurture several inquisitive minds.

(Dr Tapaswini P Sharma, Consultant, Dr Ashish Goel, Consultant; Dr AK Dewan, Sr Consultant, Surgical Oncology & Medical Director; Dr PS Choudhury, Director, Nuclear Medicine) With Best Compliments From



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