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RESEARCH ARTICLE

A COMPARATIVE STUDY OF TWO HYPOFRACTIONATED EXTERNAL BEAM RADIATION THERAPY SCHEDULES IN SYMPTOM PALLIATION IN UNRESECTABLE CARCINOMA GALLBLADDER

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Abstract

Introduction: Gallbladder cancer is a highly aggressive cancer, with majority of the patients presenting in advanced stage having a dismal prognosis.
Objective: The aim of the study, is to compare the symptom relief, loco-regional tumour response and tolerance between the two different external beam radiation therapy schedules.
Methods: A randomized study was conducted for two years including 60 patients. The patients were divided into two arms, with Arm-A receiving a total dose of 33Gy/15# and theArm-B receiving 30Gy/10#.
Results: Early tumour response was slightly better in Arm-B than in Arm-A, with 50% patients showing partial response in Arm-B in comparison to 40% in Arm-A. Symptom relief was better and statistically significant in Arm-B with respect to Arm-A. At 3 and 6 month follow up, the symptomatic relief was comparable between the two arms, with 72% patients having relief of nausea/ vomiting in Arm-B with respect to 39.1% patients in Arm-A. The weekly toxicities were almost comparable between the arms, with haematological toxicities being slightly higher in Arm-A as compared to Arm-B. Late treatment related toxicities were also higher in Arm-A as compared to Arm-B.
Conclusion: Palliative radiation therapy given to patients, over a short period of time is better in comparison to similarequivalent dose given over longer period of time in symptom palliationfor patients with unresectable gallbladder cancer.

Introduction:-

The gallbladder is a pear shaped, saccular organ situated under the liver in line with the physiologic division of the right and left lobes of the liver (Cantlie's line).[1] Gallbladder cancer (GBC) is a rapidly growingtumour with a tendency for early dissemination by direct invasion into liver, lymphatic spread, hematogenous spread and by production of peritoneal "drop metastases".[2]

GBC accounts for 80%-95% of the biliary tract cancers. An early diagnosis is essential as it progresses silently leading to a late diagnosis, which is often fatal. GBC is considered as one of the most malignant forms of cancer for which chemotherapy and radiation therapy have little effect, and radical surgery remains the most effective treatment. The prognosis for patients with advanced GBC is very poor, with a 5-year survival rate of 6%-20%.[3]

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According to GLOBOCAN 2018 data, GBC is the 22nd most common cancer, but 17th most deadly cancer worldwide. The incidence in the U.S. is lower than that around the world.[4] In India; North, East, Northeast and Central India are having a high incidence of GBC with respect to South and West India. The incidence in North India is 10-22/100000 population and is similar to that of other countries with high incidence such as in South America.[5]

The incidence of GBC correlates with the prevalence of cholelithiasis, and increases with age, with the greatest incidence in persons aged 65 years or older. The world incidence of GBC varies considerably with geographic location, with the highest incidence being in Chileans and Bolivians.[6]In India, it is one of the commonest and deadliest cancers occurring along the river basins of the Ganga and the Brahmaputra River, with a high prevalence along the Indo-Gangetic plains of northern and eastern India, especially in the states of Uttar Pradesh and Bihar.[7]

Cholelithiasis, anomalous junction of the pancreaticobiliary ducts, porcelain gallbladder, altered bile composition, congenital biliary cysts or ductal anomaly, infections, environmental carcinogens, and drugs are important risk factors that predispose to GBC.[8] Cigarette smoking, alcohol consumption and obesity may also contribute to the risk. The duration of gallstone disease, the patient's age, the size of gallstones, and possible carcinogenic effects of gallstones are important risk factors for GBC.

The clinical presentation of GBC is often vague and delayed. The most common clinical presentation is pain followed by anorexia, nausea or vomiting. In general, patients having GBC presents with symptoms like jaundice, anorexia, weight loss and they are associated with more advanced disease, which accounts for the poor prognosis.[9]

For the diagnosis of GBC, in addition to physical examination and biopsy, imaging modalities such as Endoscopic retrograde cholangiopancreatography (ERCP), MRI, CECT scan, Percutaneous cholangiography, Endoscopic ultrasonography (EUS), Magnetic resonance cholangiopancreatography (MRCP) and PET-CT scan are useful.[10]Tumour markers such as serum CEA, CA125, CA242 and CA19-9 may be elevated, but they are quite inconsistent for the diagnosis of GBC.[11]

Percutaneous FNAC or core needle biopsy are indicated for unresectable masses. Most malignant neoplasms of the gallbladder are adenocarcinomas (80%). Tumours most commonly originates from the fundus (60%). GBCs have histopathologic grading varying from G1 (well differentiated) to G4 (undifferentiated). Although the grade does not factor into staging, it has prognostic significance, with high-grade tumours having a worse prognosis.[12]

A small percentage of patients (25% only) present with stage 1 disease and they may be cured by surgery. The role for surgery in patients with stage 2 and 3 disease remains controversial. Surgical resection is the only potentially curative treatment for GBC, but even after complete resection with hepatic resection, locoregional and/or distant recurrences is very common. Adjuvant treatment modalities, such as chemoradiotherapy (CTRT) or chemotherapy (CT), are required to decrease both locoregional and distant recurrences, thereby improving survival in patients with GBC undergoing surgical resection.[13]

The majority of patients with GBC presents with advanced stage disease, with a high mortality rate. Prognostic factors for GBC include perineural invasion, liver metastasis, lymphatic invasion, possibility of curative resection, microscopic tumour, depth of invasion, degree of tumour differentiation, and metastasis to both local and distant lymph nodes.[14] Patients having locally unresectable GBC are treated by CTRT, with the standard of care for systemic CT being Cisplatin and Gemcitabine based chemotherapeutic agents.

The goal of palliative treatment in unresectable GBC are relief of pain, jaundice, pruritis, bowel obstruction, nausea/vomiting and prolongation of life. Patients who have pain from local growth may benefit from radiation therapy with or without concomitant chemotherapy. The benefits of using radiation therapy as a palliative treatment over systemic chemotherapy is that there is less systemic toxicity, less chemotherapy induced side-effects, less morbidity, better patient compliance, better tumour response and better symptom palliation. Some disadvantages of using radiation therapy are radiation induced hepatitis, renal toxicities and/or symptomatic duodenal ulcers, depending on the radiation dose given.

The aim of the study, is to compare the symptom relief, loco-regional tumour response and tolerance between two different palliative radiation therapy schedules. An equivalent dose of 30Gy in 10# vs 33Gy in 15# was used for

palliation, to reduce the radiation induced side-effects and decrease the duration of treatment period while achieving the same degree of tumour response and symptom palliation.

Methods:-

A randomized control study was conducted in the Department of Radiation Oncology, RIMS, Imphal, Manipur for two years from November, 2020 to October, 2022 consisting of 60 patients. The permission of the Research Ethics Board (REB), RIMS, Imphal, Manipur was obtained before initiating the study. Informed written consent were taken from all patients.

Inclusion criteria included patients between the age of 30-70 years, with histopathologically/ cytologically confirmed gallbladder cancer (according to AJCC 8thedition 2017) with TNM Stage 3A, 3B and 4A; having a Karnofsky Performance Status (KPS) ≥ 70%.

Exclusion criteria included pregnant and lactating mother; patients with metastasis to distant organs or previously treated with radiation therapy, chemotherapy or surgery; patients with mental disorder or deranged liver function test (i.e., 2 times more than the normal limit)

The patients were recruited in the two arms (Arm-A & Arm-B) by simple randomization method (Lottery method). Complete history and thorough physical examination were done before the start of the treatment.

Baseline investigations (before the start of treatment):

1. Complete blood count and blood biochemistry (liver function tests, kidney function tests, serum electrolytes, PT-INR, fasting and post-prandial blood sugar levels).
2. ECG, ECHO and Chest X-ray (PA view).
3. Biopsy/ FNAC of the tumour site and from the regional lymph nodes.
4. CECT scan of the whole abdomen and thorax to determine the extent of the disease and full metastatic workup.

After confirmation of the disease and proper workup, all the patients were randomized into two arms. InArm-A, patients received a total dose of 33Gy/15# for 5 days/week (i.e., 220 cGy/#) for three weeks, andinArm-B, patients received a total dose of 30Gy/10# for 5 days/week (i.e., 300 cGy/#) for two weeks.

All the patients were treated with Cobalt-60 teletherapy machine. The radiation was given to the primary tumour and regional lymphatics (porta-hepatic, pancreaticoduodenal and celiac lymph nodes) by two parallel opposed anterior and posterior portals or multiple fields according to the disease clinical target volume [CECT based radiation therapy planning was done]. Organs at risk including the spinal cord, liver, kidney and intestines were not considered to be a problem as the Biological Effective Dose (BED) was less than the respective tolerance dose.

During treatment all the patients enrolled in the study were assessed weekly for radiation therapy related side-effects and toxicities, and symptom relief, with complete blood count, liver function tests, kidney function tests, and serum electrolytes.

Post treatment evaluation:

1. The patient's symptom relief and loco-regional tumour response were assessed one month after the completion of radiation treatment for both the arms by using the RECIST CRITERIA version 1.1.
2. The early toxicity to the treatment was assessed 2 weeks after the completion of radiation treatment for both the arms by using the RTOG criteria.
3. Patients were worked up with complete history, thorough clinical examination, complete blood count, LFT, KFT, serum electrolytes, chest X-ray (PA view), CECT of the whole abdomen and tumour markers (CA 19-9, CEA) on follow up.
4. Then the patient was followed up every 3 months after the completion of radiation treatment for a minimum period of six months, to assess the patient for treatment related toxicity and symptom relief as per the RTOG criteria.

Data were collected by using structured proforma in hard and soft copy, and the collected data was entered in Microsoft Excel File for further analysis. Data analysis was done using IBM SPSS statistics version 22 (IBM Corp, 1995, 2012). (P value <0.05 was considered as statistically significant).

Results:-

A total of 60 patients were enrolled in the study, and were equally divided into two Arms (A & B). At 3 month, 7 patients were lost to follow up (4 in Arm-A and 3 in Arm-B) and the total sample size was reduced to 53 patients. At 6 month, 5 more patients were lost to follow up (3 in Arm-A and 2 in Arm-B), thus the final data was analysed for the remaining 48 patients only. Characteristics features of the patient and disease are shown in Table 1 and 2 respectively.

Table 1:- Patient characteristics (N=60)

Variables	Sub variables	Arm-A (n=30) (%)	Arm-B (n=30) (%)
Median age in years		63 years	
Sex	**Male**	6 (20%)	4 (13.3%)
	Female	24 (80%)	26 (86.7%)
KPS	**90%**	5 (16.7%)	6 (20%)
	80%	12 (40%)	11 (36.7%)
	70%	13 (43.3%)	13 (43.3%)
Risk factors	**Smoking**	8 (26.7%)	12 (40%)
	Alcohol	12 (40%)	10 (33.3%)
	Gall stones	19 (63.3%)	20 (66.7%)

Table 2:- Disease characteristics (N=60)

Variables	Sub variables	Arm-A (n=30) (%)	Arm-B (n=30) (%)
Clinical presentation	**Jaundice**	13 (13.3%)	15 (50%)
	Upper abdominal pain	16 (53.3%)	13 (43.3%)
	Palpable abdominal mass	20 (66.7%)	21 (70%)
	Nausea /Vomiting	5 (16.7%)	4 (13.3%)
HPE	**Adenocarcinoma**	28 (93.3%)	28 (93.3%)
	Squamous cell carcinoma	2 (6.7%)	2 (6.7%)
Stage	**3A**	7 (23.3%)	5 (16.7%)
	3B	13 (43.3%)	12 (40%)
	4A	10 (33.4%)	13 (43.3%)

It was observed that all the biochemical parameters [total bilirubin (T.B.), aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT)] were elevated in most of the patients before the start of radiation treatment. Weekly comparison of these parameters in between the two arms during the treatment and at 4 weeks after the completion of radiation therapy, was statistically insignificant.

Weekly comparison of anaemia between the two arms during the treatment showed that there was mild anaemia in both the arms. After 2 weeks of completion of radiation treatment, 7 patients in Arm-A and 2 patients in Arm-B had Grade 1 anaemia, with Grade 2 anaemia seen only in 1 patient in Arm-A, which was statistically insignificant. (RTOG Criteria)

Weekly comparison of leukopenia in between the two arms during the treatment showed that there was mild grade of leukopenia in both the arms. After 2 weeks of completion of radiation therapy, 9 patients (30%) in Arm-A and 5 patients (16.7%) in Arm-B had different grades of leukopenia, which was statistically insignificant.

Weekly comparison of thrombocytopenia in between the two arms during the treatment showed that there was mild grade of thrombocytopenia in both the arms. After 2 weeks of completion of radiation therapy, 13 patients (43.3%) in Arm-A and 8 patients (26.7%) in Arm-B had different grades of thrombocytopenia, which was statistically insignificant.

Table 3 shows the weekly comparison of symptom relief between the two arms during the treatment and at 4 weeks after the completion of radiation therapy. The patients were assessed subjectively and clinically. A p-value of 0.007 and 0.028, for jaundice and pruritus respectively, at 1 week of radiation therapy; anda p-value of 0.030 and 0.035, for upper abdominal pain and nausea/ vomiting respectively, at 4 weeks after the completion of radiation therapy

shows that the result is statistically significant (Improved = decrease of symptoms or bringing it nearer to standard, worsened = increase of symptoms or deterioration of health)

Table 3:- Comparison of symptom relief (N=60)

Symptom	Week	Symptom relief	Arm-A (n=30) (%)	Arm-B (n=30) (%)	p-value
Upper Abdominal pain/ Right hypochondrium pain	1	Same	19 (63.3%)	17 (56.7%)	0.598
		Improved	11 (36.7%)	13 (43.3%)	
		Worsened	0	0	
	2	Same	13 (43.7%)	13 (43.7%)	1.000
		Improved	17 (56.7%)	17 (56.7%)	
		Worsened	0	0	
	3	Same	4 (13.3%)	-	-
		Improved	26 (86.7%)	-	
		Worsened	0	-	
	6 (Arm B)/ 7 (Arm A)	Same	0	6 (20%)	**0.030**
		Improved	23 (76.7%)	20 (66.7%)	
		Worsened	7 (23.3%)	4 (13.3%)	
Jaundice (yellowish discolouration of sclera)	1	Same	27 (90%)	18 (60%)	**0.007**
		Improved	3 (10%)	12 (40%)	
		Worsened	0	0	
	2	Same	21 (70%)	16 (53.3%)	0.184
		Improved	9 (30%)	14 (46.7%)	
		Worsened	0	0	
	3	Same	9 (30%)	-	-
		Improved	19 (63.3%)	-	
		Worsened	2 (6.7%)	-	
	6 (Arm B)/ 7 (Arm A)	Same	3 (10%)	10 (33.3%)	0.088
		Improved	21 (70%)	15 (50%)	
		Worsened	6 (20%)	5 (16.7%)	
Pruritus	1	Same	27 (90%)	20 (66.7%)	**0.028**
		Improved	3 (10%)	10 (33.3%)	
		Worsened	0	0	
	2	Same	20 (66.7%)	16 (53.3%)	0.292
		Improved	10 (33.3%)	14 (46.7%)	
		Worsened	0	0	
	3	Same	12 (40%)	-	-
		Improved	18 (60%)	-	
		Worsened	0	-	
	6 (Arm B)/ 7 (Arm A)	Same	6 (20%)	8 (26.7%)	0.331
		Improved	22 (73.3%)	17 (56.7%)	
		Worsened	2 (6.7%)	5 (16.6.%)	
Nausea/ Vomiting	1	Same	21 (70%)	17 (56.7%)	0.284
		Improved	9 (30%)	13 (43.3%)	
		Worsened	0	0	
	2	Same	9 (30%)	13 (43.3%)	0.284
		Improved	21 (70%)	17 (56.7%)	
		Worsened	0	0	
	3	Same	2 (6.7%)	-	-
		Improved	28 (93.3%)	-	
		Worsened	0	-	
	6 (Arm B)/ 7 (Arm A)	Same	0	6 (20%)	**0.035**
		Improved	23 (76.7%)	19 (63.3%)	
		Worsened	7 (23.3%)	5 (16.7%)	

Bowel movement (Diarrhoea)	**1**	**Same**	24 (80%)	20 (66.7%)	0.243
		Improved	6 (20%)	10 (33.3%)	
		Worsened	0	0	
	2	**Same**	20 (66.7%)	15 (50%)	0.190
		Improved	10 (33.3%)	15 (50%)	
		Worsened	0	0	
	3	**Same**	12 (40%)	-	-
		Improved	18 (60%)	-	
		Worsened	0	-	
	6 (Arm B)/ 7 (Arm A)	**Same**	4 (13.3%)	10 (33.3%)	0.181
		Improved	20 (66.7%)	16 (5.3%)	
		Worsened	6 (20%)	4 (13.4%)	

Table 4 shows the comparison of overall treatment response between the two arms after 1 month of completion of treatment. All the 60 patients were available for assessment at the end of 1 month. (RECIST Criteria)

Table 4:- Treatment response (N=60)

Response	Arm-A (n=30) (%)	Arm-B (n=30) (%)	p-value
Partial response	12 (40%)	15 (50%)	0.225*
Stable disease	10 (33.3%)	10 (33.3%)	
Progressive disease	8 (26.7%)	5 (16.7%)	
Total	30	30	

At 3 month follow up, only 53 patients came for check-up, with 7 patients lost to follow up (4 patients in Arm-A and 3 patients in Arm-B); and at 6 month follow up, only 48 patients came for check-up, with 12 patients lost to follow up (7 patients in Arm-A and 5 patients in Arm-B).

Table 5 shows the comparison of symptom relief between the two arms on follow up at month 3 and 6. The patients were assessed subjectively and clinically. Both at 3 month and 6 month follow up, there was not that much difference in symptom relief in between the two arms; except for relief of nausea/ vomiting at 6 month follow up, were 18 patients had relief of nausea/ vomiting in Arm-B with respect to 9 patients in Arm-B. A p-value of 0.022 at 6 month follow up shows that the result is statistically significant. The other results were found out to be statistically insignificant.

Table 5:- Symptom relief between the two arms on follow up (Month 3 & 6)

Symptom	Month	Symptom relief	Arm-A (%)	Arm-B (%)	p-value
Upper Abdominal pain/ Right hypochondrium pain	**3 (n=53)**	**Same**	1 (3.8%)	1 (3.7%)	0.878
		Improved	18 (69.3%)	17 (63%)	
		Worsened	7 (26.9%)	9 (33.3%)	
	6 (n=48)	**Same**	1 (4.3%)	1 (4%)	0.971
		Improved	13 (56.5%)	15 (60%)	
		Worsened	9 (39.2%)	9 (36%)	
Jaundice	**3 (n=53)**	**Same**	1 (3.8%)	1 (3.7%)	0.994
		Improved	16 (61.5%)	17 (63%)	
		Worsened	9 (34.7%)	9 (33.3%)	
	6 (n=48)	**Same**	1 (4.3%)	0	0.350
		Improved	10 (43.5%)	15 (60%)	
		Worsened	12 (52.2%)	10 (40%)	
Pruritus	**3 (n=53)**	**Same**	4 (15.4%)	1 (3.7%)	0.286
		Improved	17 (65.4%)	18 (66.7%)	
		Worsened	5 (19.2%)	8 (29.6%)	
	6 (n=48)	**Same**	1 (4.3%)	1 (4%)	0.391
		Improved	17 (73.9%)	18 (72%)	

Symptom	Month	Symptom relief	Arm-A (%)	Arm-B (%)	p-value
		Worsened	5 (21.8%)	6 (24%)	
Nausea/ Vomiting	**3 (n=53)**	**Same**	1 (3.8%)	0	0.517
		Improved	14 (53.8%)	17 (63%)	
		Worsened	11 (42.4%)	10 (37%)	
	6 (n=48)	**Same**	0	0	**0.022**
		Improved	9 (39.1%)	18 (72%)	
		Worsened	14 (60.9%)	7 (28%)	
Bowel movement (Diarrhoea)	**3 (n=53)**	**Same**	1 (3.8%)	1 (3.7%)	0.924
		Improved	16 (61.5%)	18 (66.7%)	
		Worsened	9 (34.7%)	8 (29.6%)	
	6 (n=48)	**Same**	0	1 (4%)	0.266
		Improved	10 (43.5%)	15 (60%)	
		Worsened	13 (56.5%)	9 (36%)	

Late complications were assessed at the 3rd and 6th month after completion of radiation. It was observed that out of 53 patients; 3 patients had skin reaction, 18 patients had liver toxicity, 21 patients had small/ large intestine toxicity, and 16 patients had kidney function derangements at 3 month follow up. At 6 month follow up, out of 48 patients; 5 patients had skin reactions, 28 patients had liver toxicity, 22 patients had small/ large intestine toxicity, and 22 patients had kidney function derangements. (RECIST Criteria)

Discussion:-

Historically, GBC has carried a poor prognosis. Elderly patients often present with medical and physiological challenges that makes the selection of their optimal treatment difficult, and they are at risk of both empirical undertreatment resulting in poor survival or excessive toxicity from standard therapy. Some of the data available today is based on retrospective studies of trials in patients with good performance status.

In this study, 33Gy/15# (Arm-A) was compared with 30Gy/10# (Arm-B), both having equal BED, for symptom palliation and to decrease the duration of treatment period while achieving the same degree of tumour response and symptom palliation.

In this study, the median age of the patients was 63 years. Out of 30 patients in Arm-A, 20% were males and 80% were females. In Arm-B, 13.3% and 86.7% of patients were males and females respectively. The male to female ratio in this study was 1:5. These findings were similar to a study performed by Nervi F et al[15] where the mean age was 66.11 years and the median age was 60 years, with the male to female ratio being 1:4.

In this study, majority of the patients (39 patients) had history of cholelithiasis (19 patients in Arm-A and 20 patients in Arm-B). On sub-group analysis, 31 female patients and 8 male patients had history of cholelithiasis. These findings were similar to a study performed by Dwivedi S et al[16] where cholelithiasis was frequently associated with GBC in up to 60%-70% patients.

In this study, 46.7% patients presented with jaundice, 48.4% patients complained of only upper abdominal or right hypochondrium pain, and 68.3% patients presented with palpable abdominal mass in right hypochondrium. Similar finding was noted in a study by Chattopadhyay TK et al[17] where majority of the GBC patients presented with jaundice, itching, pain, and palpable mass in right hypochondrium.

Adenocarcinoma was the most common histologic subtype in this study accounting for 28 patients (93.3%) each in both the Arms. On subgroup analysis, 35.7% patients had well differentiated, 41.1% patients had moderately differentiated, and 23.2% patients had poorly differentiated adenocarcinoma. Similar finding was reported by Kanthan R et al[18] which showed adenocarcinoma as the most common histologic type, accounting for 98% of all gallbladder tumours.

The patient characteristics of both the Arms were well balanced without any statistically significant differences in Age, Sex, KPS, HPE and Stage.

In this study, after 1 month of treatment with radiation therapy, there was marked improvement in all the symptoms in both the arms. Arm-A showed improvement of jaundice in 21 patients (70%), relief from upper abdominal pain in 23 patients (76.7%), decreased pruritus in 22 patients (73.3%), decreased nausea/ vomiting in 23 patients (76.7%) and improved bowel movement in 20 patients (66.7%). Arm-B also showed improvement of jaundice in 15 patients (50%), relief of upper abdominal pain in 20 patients (66.7%) and decreased nausea/ vomiting in 19 patients (63.3%). Patients complaining of worsening of clinical symptoms after 1 month of treatment were more common in Arm-A with respect to Arm-B. These findings were similar to a study conducted by Smoron et al[19]where patients showed good symptom palliation along with shrinkage of abdominal mass in patients treated with radiation therapy.

Early tumour response was assessed after one month of completion of radiation therapy radiologically by CECT scan of whole abdomen. In Arm-A,40% patients had Partial response and33.3% had Stable disease. In Arm-B,50% patients had Partial response and33.3% had Stable disease. Disease progression was higher in Arm-A (26.7%) as compared to Arm-B (16.7%). These findings were similar to a study conducted by Uno et al[20] which showed patients treated with EBRT showed slightly improved survival, with Partial response being 50% and patients with Stable disease being 33.3% in the radiation arm. Hou et al[21] in a case report also suggested that radiotherapy may also be used in palliative management of advanced gallbladder carcinoma, and the patient was treated with radiotherapy alone, and showed marked improvement in symptoms with partial response to radiation.

Early treatment toxicities were compared in between the two arms during radiation therapy and at 2 weeks after completion of radiation therapy. Haematological toxicity was the most common toxicity in this study. During radiation therapy the early toxicity was comparable in both the Arms. At 2 weeks following radiation therapy, 26.7% patients in Arm-A and 6.7% in Arm-B had anaemia; 30% patients in Arm-A and16.6% in Arm-B had leukopenia; and43.3% patients in Arm-A and 26.6% in Arm-B had thrombocytopenia. Patients in Arm-A had more toxicity with respect to Arm-B, the exact reason for it is not known, but is believed to be due to slightly higher radiation dose in Arm-A with respect to Arm-B.

There was marked improvement in the serum levels ofT.B., SGOT, SGPT, ALP and GGT; with patients in Arm-B having better response with respect to patients in Arm-A. These findings were similar to a study conducted by Omar et al[22] on the role of EBRT in the management of GBC, which showed that patients treated with EBRT alone showed better improvement in the biochemical parameters as compared to the patients treated with chemotherapy alone or along with radiation therapy.

At 3 and 6 month follow up, the total sample size was reduced to 53 and 48 patientsrespectively.

Symptom relief assessed at both 3- and 6-month follow up was comparable in between the two arms, with more patients having symptom relief in Arm-B with respect to Arm-A. Relief from nausea/ vomiting was seen in 72% patients in Arm-B with respect to 39.1% in Arm-A, at 6 month follow up. Late treatment related toxicity with respect to skin reactions, liver and kidney damage, and bowel movements; were assessed at 3 and 6 months, and were also comparable in between the arms, with patients in Arm-A having more toxicity in comparison to Arm-B. These findings were similar to a study conducted by Eleftheriadis et al[23] where the patient was treated with a total dose of 30Gy in 10# and showed marked improvement in symptoms with less toxicity on follow up.

This study was based on the fact that patients with unresectable GBC are incurable and are treated with a palliative intent. According to this study, patients treated with 30Gy/10# (i.e., Arm-B) had similar treatment response and toxicity profile to patients treated with 33Gy/15# (i.e., Arm-A), with patients in Arm-B having slightly better symptomatic relief and biochemical profile in comparison to patients in Arm-A. Thus, Arm-B was found to be slightly better thanArm-A, in achieving similar degree of benefits, but with lesser treatment time.

One of the major limitations of this study is that due to the time constraint, longer duration of follow-up could not be reported among the study population. This could have resulted in the absence of significant difference between the groups. Another limitation is that, the sample size was less to arrive at the generalizability. This study could be considered as a preliminary step, but further studies at a larger scale need to be conducted to achieve a generalability.

Conclusion:-

The management of unresectable GBC is quite challenging, with different techniques being tried in controlling the disease progression and symptom palliation. Treatment of unresectable GBC usually consists of various palliative strategies which provide only a modest survival benefit. The early tumour response rate of the Arm-B was slightly better as compared to the Arm-A. Symptom relief was better and was found to be statistically significant in Arm-B with respect to Arm-A in between two arms during the radiation treatment, and at 4 weeks after the completion of radiation treatment. At 3 and 6 month follow up, the symptomatic relief was comparable in between the two arms, with 72% patients having relief of nausea/ vomiting in Arm-B with respect to 39.1% patients in Arm-A.

From this study, it may be concluded that palliative radiation therapy given to patients, over a short period of time is better in comparison to similar biological equivalent dose given over longer period of time in symptom palliation of patients with unresectable GBC; as it decreases the treatment time, decreases the hospital stay, better patient compliance and greater patient's turnover for radiation treatment; while having better or similar symptom palliation and lesser treatment toxicities. Further studies are needed on a multicentre level with a larger patient population and longer duration of follow-up to add more evidence to the available literature.

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