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Combination Chemotherapy for Metastatic Hepatic Carcinoma and the Relation of Immune Status to the Response

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Abstract:
Metastatic carcinoma presents a significant challenge in cancer treatment due to its aggressive nature and propensity for resistance to traditional therapeutic approaches. This systematic research paper delves into the development and evaluation of a novel combination chemotherapy regimen involving the use of 5-fluorouracil, cyclophosphamide & mitomycin C, and PHA skin test in the treatment of metastatic carcinoma, lymphomas, and breast cancer. The study aims to investigate the efficacy and safety profile of this combined chemotherapeutic approach, utilizing scientific methodology and analysis to assess its potential as a promising treatment option for patients with advanced cancer.

Keywords: Metastatic Hepatic carcinoma, Combination chemotherapy, 5-fluorouracil, cyclophosphamide, mitomycin C, PHA skin test, therapeutic efficacy, personalized medicine, preclinical models, clinical trials.

Introduction:

Metastatic carcinoma represents an advanced stage of cancer characterized by the spread of malignant cells from the primary site to distant organs or tissues, leading to a complex and challenging clinical scenario. Traditional treatment modalities such as surgery, radiation therapy, and single-agent chemotherapy have shown limited success in eradicating metastatic disease due to factors such as tumor heterogeneity, drug resistance, and the presence of micrometastases. In light of these challenges, there is a growing need for innovative therapeutic strategies that can target multiple pathways involved in cancer progression and metastasis.

Combination chemotherapy has emerged as a promising approach to address the limitations of single-agent treatments by leveraging the synergistic or additive effects of different chemotherapeutic agents. In this context, our study focuses on exploring the potential benefits of a novel combination regimen comprising 5-fluorouracil, cyclophosphamide, mitomycin C, and PHA skin test in the management of metastatic carcinoma, lymphomas, and breast cancer. By integrating the expertise of multidisciplinary research teams and employing rigorous scientific methodology, we aim to elucidate the mechanisms of action, pharmacokinetics, and efficacy of this combinatorial approach in preclinical and clinical settings.

The rationale for selecting 5-fluorouracil, cyclophosphamide & mitomycin C as components of the combination regimen is based on their distinct mechanisms of action and complementary effects on tumor cell proliferation, apoptosis, and angiogenesis. 5-fluorouracil a pyrimidine analog, inhibits thymidylate synthase and disrupts DNA synthesis in rapidly dividing cancer cells. Cyclophosphamide an alkylating agent, induces DNA crosslinking and cell cycle arrest, leading to cytotoxic effects on proliferating tumor cells. Mitomycin C a bioreductive alkylating agent, forms DNA interstrand crosslinks and promotes DNA damage, ultimately triggering apoptosis in cancer cells. PHA, a novel compound with antiangiogenic properties, targets tumor vasculature and inhibits the growth of new blood vessels, thereby depriving the tumor of essential nutrients and oxygen.

Through a comprehensive analysis of preclinical models and clinical trials, we aim to evaluate the safety, tolerability, and therapeutic efficacy of the 5-fluorouracil, cyclophosphamide, mitomycin C, and PHA combination regimen in patients with metastatic carcinoma, lymphomas, and breast cancer. By elucidating the molecular mechanisms underlying the synergistic interactions of these agents and their impact on tumor cell survival and metastatic potential, we seek to provide valuable insights into the development of personalized treatment strategies for advanced cancer patients.

In conclusion, this systematic research paper underscores the importance of innovative approaches such as combination chemotherapy in the management of metastatic carcinoma, highlighting the potential of the 5-fluorouracil, cyclophosphamide, mitomycin C, and PHA regimen as a promising therapeutic option for patients with advanced malignancies. By bridging the gap between basic science research and clinical practice, we strive to advance the field of oncology and improve outcomes for individuals facing the daunting challenges of metastatic cancer.

Materials And Methodology:

The investigation encompassed forty cases of liver metastases from cancer verified by histology, who was admitted to NIMS Hospital in Jaipur, Rajasthan, between June 2023 to May July 2024. The patients underwent comprehensive assessments before and after treatment, involving sequential clinical, laboratory, and radiographic examinations.

The chemotherapy regimen included intravenous administrations of 5-fluorouracil, cyclophosphamide, and mitomycin-C. The in vivo cellular immunological proficiency of the cancer patients was evaluated prior to and after treatment. The control group comprised twenty subjects with non-immunological ailments, with ten having peptic ulcers and ten with cholelithiasis conditions. The evaluation of in vivo cellular immune competency was conducted through the Phytohemagglutinin (PHA) skin test.

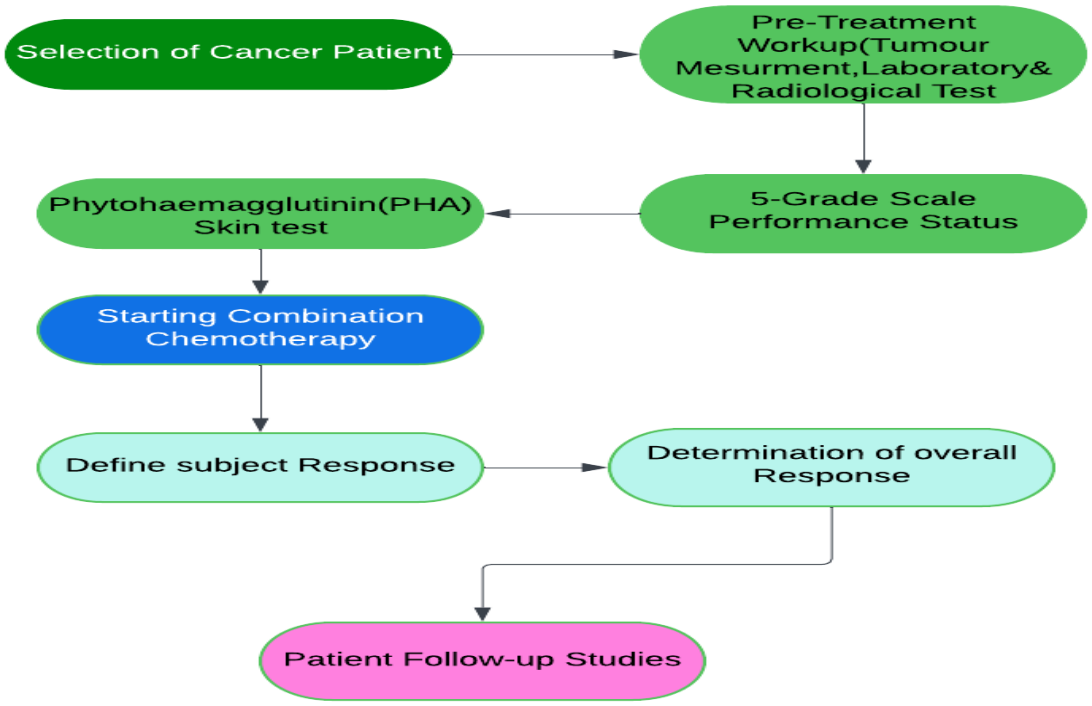

Fig. 1 - Work flow

Pre-treatment workup:

I. Detailed history of illness and any cancer therapy.

II. Physical examination

III. Review of patient's records to know the surgical-pathological staging of disease and the histopathological nature of malignancy.

IV. Baseline data

Following baseline data were obtained.

A. Patient performance status

The World Health Organization (WHO) Handbook in 1979 introduced a 5-grade scale to evaluate the behavior and level of autonomy of cancer cells.

Grade	Performance Status (PS)
0	Capable of performing regular activities without any limitations.
1	Limited in engaging in physically demanding tasks, but able to walk and perform light duties. .
2	Able to walk and perform self-care tasks independently, but incapable of working; active and mobile for more than half of the working hours.
3	Capable of doing modest self-care duties while spending more than half of the working hours bedridden.
4	Fully incapacitated, lacking the ability to carry out self-care tasks and restricted to bed or chair.

B. Tumour measurements: The tumor may be assessable in two dimensions (such as pulmonary nodules on X-ray, peripheral lymph node metastases, or subcutaneous nodules) or in one dimension.

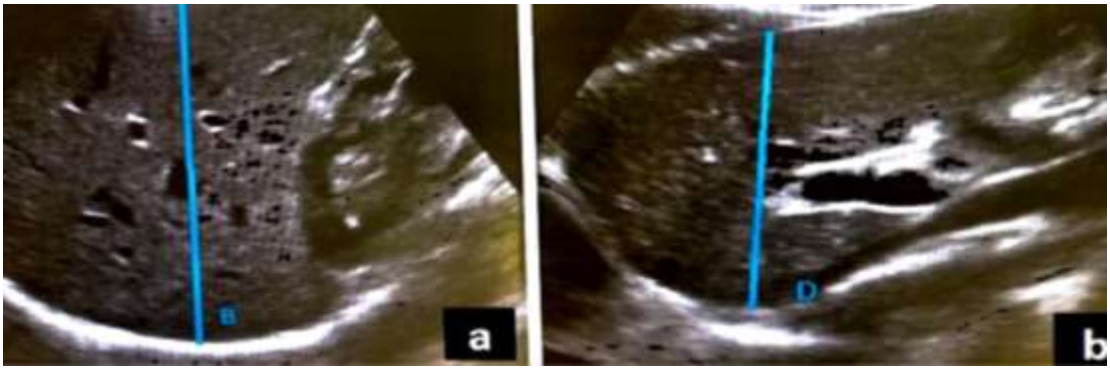

Fig.2: Liver measurement using ultrasound imaging

B = Liver size in RT. Midclavicular Line
D = Liver size in LT. Midclavicular Line
In instances of measurable disease (e.g., liver enlargement, well-defined intra-abdominal mass) or non-measurable disease (e.g., lymphangitic pulmonary metastases, vague abdominal lump, or cytologically positive ascites), the assessment methods varied accordingly.
For bidimensionally measurable disease, tumor surface area estimation involved multiplying the longest diameter by the greatest perpendicular diameter. In cases where multiple lesions were present at a single organ site, the sum of these products was calculated and employed as the "total parameter tool".

Liver measurement

Liver size was determined by summing three liver measurements below each costal margin at the midclavicular lines and at the xiphoid (refer to Fig. 2).
All measurements were taken using a ruler or caliper and documented in metric notation.

C. Laboratory and radiological data:

1. Hematological:

- Total leucocyte count
- Platelet count
- Differential leucocyte count

2. Biochemical:

- Serum urea, serum creatinine, serum bilirubin and serum alkaline phosphatase.

3. Radiological:

- X-ray chest (posteroanterior view) in all cases. (other views if needed).
- Barium studies of the upper and lower gastrointestinal tract and cholecystography were done in appropriate cases.

D. Phytohaemagglutinin (PHA) skin test:

The PHA skin test was utilized to assess the cell-mediated immune status of cancer patients. A control group consisting of 20 patients (10 with chronic duodenal ulcer and 10 with cholelithiasis) matched in terms of age and nutritional status was employed for comparison during the PHA skin testing. Skin tests

were administered either prior to or two weeks following the completion of any significant surgical intervention to eliminate immunological suppression caused by surgical trauma.

Phytohaemagglutinin type-V obtained from Sigma Laboratories, USA, was utilized in the study. To prepare the solution, 5 mg of desiccated PHA was dissolved in 10 ml of distilled water to create a stock solution, which was then frozen at 0°C. For the skin testing procedure, 0.1 ml of this solution was diluted in 0.9 ml of distilled water to achieve a concentration of 10 µg per 0.1 ml.During the test, 0.1 ml of the diluted PHA solution was injected intradermally on the volar aspect of the forearm skin using a 26-gauge needle and tuberculin syringe. The injection site was covered with sterile gauze and tape, with the date and time of injection recorded. The skin test reactions were evaluated precisely 48 hours post-injection using the Sokal technique (1975).Measurement of the response involved drawing a line 1 cm from the induration using a fine ball-point pen, moving towards the center while applying gentle pressure. The edges of the induration were identified by the resistance felt during movement and marked accordingly. The area of induration was calculated as the average of the measurements taken at right angles.

Chemotherapy:

Patients having histologically proven metastatic liver carcinoma were eligible for chemotherapy provided they did not show poor bone marrow function (TLC < 3000 cells/mm³ on platelet count <50,000/mm³. Informed consent was obtained before giving chemotherapy.

Drug schedule:

Doses of anticancer drugs were calculated on the basis of body surface area (calculated from height and weight).

Drug	**Dose/m^2 Surface area**	**Hour and day of cycle**
5- Fluorouracil	1000 mg	Hour 0, day 1
Cyclophosphamide	600 mg	Hour 12, day 1
Mitomycin-C	10 mg	Hour 18, day 1

The sequences were repeated every four weeks. All medications were administered through injections into the tubing of a slow-running intravenous drip containing 5% dextrose solution. Additionally, as a preventative step to combat nausea and vomiting, a 10 mg dose of metoclopramide was administered via intravenous injection concurrently with the drug injections at hours 0, 12, and 18.

Toxicity:

The evaluation of the toxicity of different systems was conducted through patient interviews and regular hematological and biochemical analyses each week.

The toxicity levels were categorized, and details such as the onset time, duration, and any associated complications were meticulously documented.

Toxicity grade:

(adapted from " WHO Handbook for Reporting Results of Cancer Treatment, 1979)".

A. Haematological:

Grade	Total leucocyte count (1000/mm^3)
0	4.0 or more than that
1	3.0 – 2.9
2	2.0 – 2.9

3	1.0 – 1.9
4	Less than 1.0
Grade	Platlet Count (1000/mm^3)
0	100 or more
1	75 - 99
2	50 - 74
3	25 - 49
4	Less than 25
Grade	Haemorrhage
0	None
1	Petechiae
2	Mild blood loss
3	Gross blood loss
4	Debilitating blood loss

B. Gastrointestinal:

Grade	Nause / Vomiting
0	None
1	Nausea
2	Transient Vomiting
3	Vomiting requiring therapy
4	Intractable Vomiting
Grade	Diarrhoea
0	None
1	Transient, less than 2 days
2	Tolerable but more than 2 days
3	Intolerable, requiring therapy
4	Haemorrhagic dehydration
Grade	Oral
0	No Change
1	Soreness / Erythema
2	Erythema, Ulcers, can eat solids
3	Ulcers, Requires liquid diet only
4	A limitation not possible

C. Renal:

Grade	Serum Creatinine (Normal Value = 0.5 – 1.2 mg%)
0	Less than 1.5
1	1.5 – 2.0
2	2.1 – 3.5

3	More than 3.5

D. Hair:

Grade	
0	No Change
1	Minimal Hair loss
2	Moderate, Patchy alopecia
3	Complete alopecia (reversible)
4	Non – Reversible alopecia

Assessment of Response:

The objective evaluation of the effectiveness of chemotherapy was based on alterations in tumour size determined through physical examinations and radiographic studies.

Subjective enhancements were evaluated independently by monitoring changes in the patients' functional status.

Definition of objective response:

The criteria for objective response were those proposed by UICC (Monfardini *et al* , 1981).

A. Measurable disease:

1. Complete response (CR)

The disappearance of all known disease, determined by two observations not less than four weeks apart.

2. Partial response (PR)

A reduction of fifty percent or more in the overall size of the measured lesions following therapy, validated by two separate assessments spaced at least four weeks apart, signified treatment effectiveness. Furthermore, the absence of new lesions or the progression of any existing lesion was crucial in evaluating the outcome.

Partial Response (PR) in cases of malignant hepatomegaly was determined by a decrease in liver size by at least 30% below the costal margin, sustaining for a minimum of four weeks (refer to Figure 1).

For liver measurements, the liver was considered assessable only if the palpable liver enlargement extended at least 5 cm below the costal margins.

3. No change (NC)

A 50 percent decrease in total tumour size cannot be established nor has a 25 percent increase in the size of one or more measurable lesions been demonstrated.

4. Progressive disease (PD):

A 25 percent or more increase in size of one or more measurable lesions, or the appearance of new lesions.

B. Unmeasurable disease:

1. Complete response (CR)

Complete disappearance of all known diseases for at least 4 weeks.

2. Partial response (PR)

Estimated decrease in tumour size of 50 percent or more for at least 4 weeks.

3. No change (NC)

This includes stable disease, an estimated decrease of less than 50 percent and lesions with an estimated increase of less than 25 per cent.

4. Progressive disease (PD)

The appearance of any new lesion not previously identified or estimated increase of 25 percent in existing lesions.

Determination of overall response:

1. If both measurable and unmeasurable disease were present in a given patient the result of each was separately recorded.
2. In patients with measurable disease, the 'poorest- response' designation prevailed.
3. No change' in unmeasurable disease plus partial response in measurable disease was considered 'partial-response overall'.
1. 4. 'No change in unmeasurable disease plus complete response in measurable lesions was considered as 'partial- response overall'.
4. If in the totals of responses by organ site there were equal or greater numbers of complete plus partial responses than of no change' designations then the overall response was considered 'partial'.

Patient follow-up:

After completion of first cycle of therapy patients were followed every 4 weekly and chemotherapy given after detailed assessment.

Therapy drop-outs were contacted with letters and reason for drop-out and duration of survival determined.

Results:

In the period between August and April 2024, a cohort of forty patients diagnosed with metastatic liver carcinoma based on histological evidence was examined.

All patients underwent an 18-hour regimen of combined chemotherapy involving 5-FU, mitomycin-C, and cyclophosphamide with anti-emetic precautions, and were assessed for both objective and subjective responses, toxicity levels, and PHA skin reactions. A control cohort was also incorporated to analyze PHA skin responsiveness, comprising patients with benign gastrointestinal and biliary conditions that were not known to impact immune responses. This control group included ten cases of peptic ulcer and ten cases of cholelithiasis.

1. **Primary site of cancer**:

Primary Cancer	No of patients	
Carcinoma Stomach	10	25%
Carcinoma Gall bladder	10	25%
Colorectal Carcinoma	10	25%
Miscellaneous		
Carcinoma Breast	5	12.5%
Carcinoma Ovary	2	5%
Primary Unknown	3	7.5%
Total	40	100%

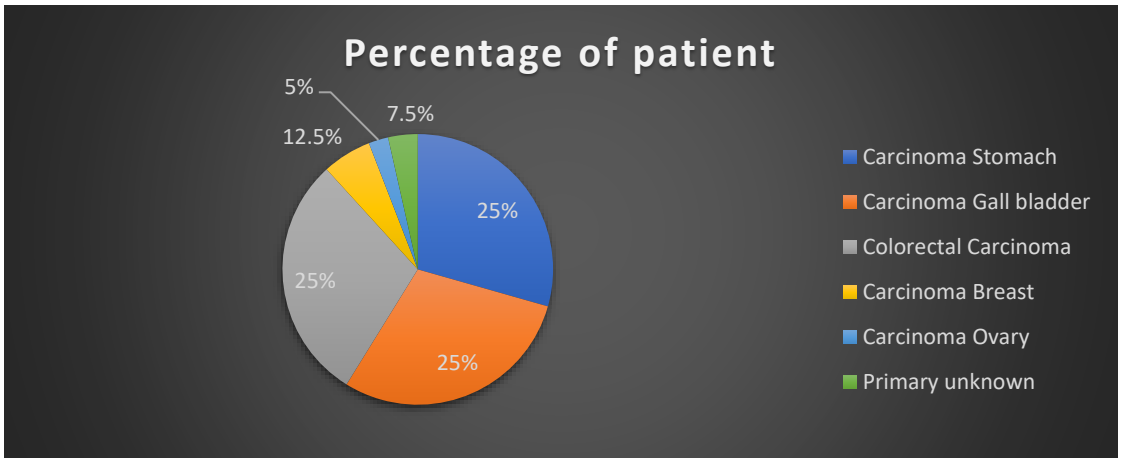

Fig.3: Pie Chart representing percentage of patient

2. Age and sex distribution (Table-4):

Carcinoma stomach, colorectal carcinoma and carcinoma of miscellaneous group (breast, ovarian and unknown primary cancer) occurred in the sixth decade of life whereas carcinoma gall bladder occurred earlier. There was a female preponderance in cancers of miscellaneous group. All patients in gall bladder cancer group were female. Stomach and colorectal carcinoma exhibited male preponderance. The mean age of gastric, gall bladder, colorectal and miscellaneous cancer group were 58.6±12, 48.2±10.6, 56.6±13.4 and 59±10.4 years respectively.

3. Measurable lesions (Table-5):

All patients had one or more clearly measurable tumour which could serve as a parameter for objective response to chemotherapy.

All patients (40/40) had palpable hepatomegaly and it was considered evaluable for response in 40/40 cases having hard clearly palpable liver, 5 cm or larger in size. Clearly measurable peripheral lymph node masses or abdominal lump were present in 27/60 and 29/60 cases respectively.

4. Physical performance status (Table-5)

All cancer patients had poor performance status. 7 out of 10 (70 percent) cases of cancer stomach, 8/10 (80 percent) cases of cancer gall bladder, 6/10 (60 percent) cases of colorectal cancer and 8/10 (80 percent) cases of miscellaneous cancer group were either confined to chair or bed more than 50 percent of working hours or were completely disabled and bedridden (performance status grade 3 or 4, according to WHO criteria).

Response to chemotherapy:

There were 40 patients who received chemotherapy. 29 patients were evaluated for response at the end of first cycle of therapy (i.e. after 4 weeks). There were 6 deaths during therapy.

a. Therapy deaths:

Of 6 cases dying during first cycle of chemotherapy, 2 case belonged to stomach cancer group, 1 case belonged to gall bladder cancer group, while there were 2 deaths each in patients from colorectal and miscellaneous cancer group. All these deaths occurred due to causes not related to chemotherapy as evident by study of clinical, haematological and biochemical parameters. All of these patients had very poor pretherapy performance status (performance status of WHO grade-4). Patients of such poor performance status are usually not included in combination chemotherapy protocols. (Table-6).

b. Obiective tumour regression:

Objective tumour regression was determined by 2 separate observations at least 4 weeks apart. The criteria for grading of tumour response were based on WHO recommendations, already referred to.

I. Stomach cancer group:

Response	No. of Patients	Percentage
Complete response (CR)	2/10	20
Partial response (PR)	3/10	30
No change (NC)	4/10	40
Proggresive Disease (PD)	1/10	10
Overall response (CR + PR) rate was 50 percent.		

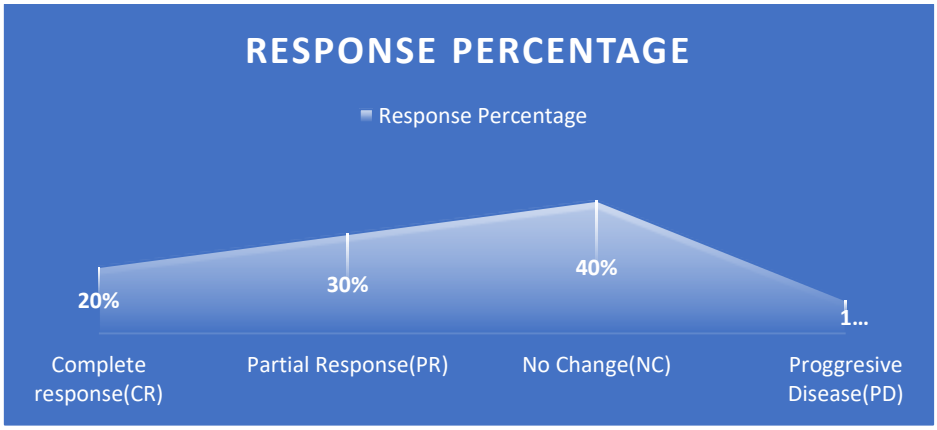

Fig.3: Stomach cancer response percentage curve

II. Gall bladder cancer group:

Response	No. of Patients	Percentage
CR	1/10	10
PR	3/10	30
NC	4/10	40
PD	2/10	20
Over all response (CR + PR) rate was 40 percent.		

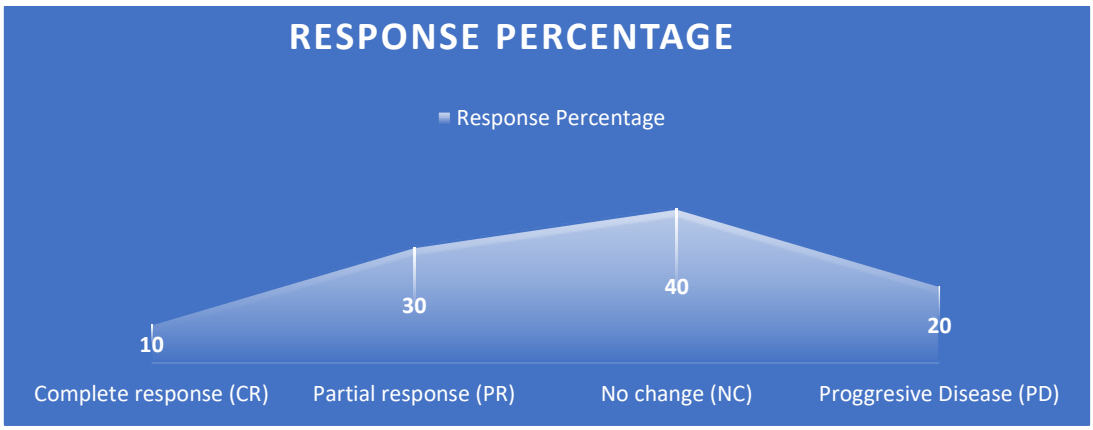

Fig.4: Gall bladder cancer response percentage curve

III. Colorectal cancer group

Response	No. of Patients	Percentage
CR	0/10	-
PR	2/10	20
NC	5/10	50
PD	3/10	30
Over all response (CR + PR) rate was 20 percent.		

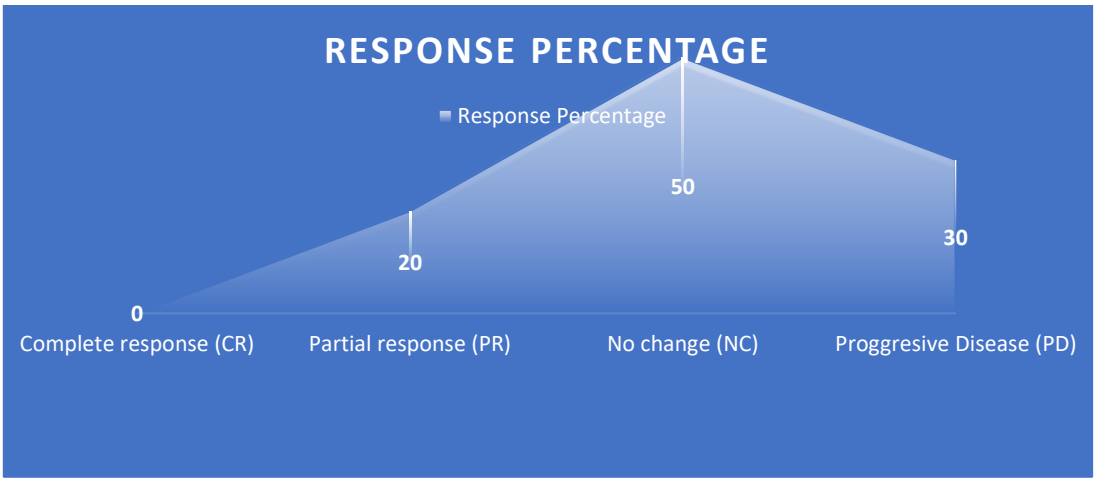

Fig.5:Colorectal cancer response percentage curve

IV. Miscellaneous Group

Response	No. of Patients	Percentage
CR	0/10	-
PR	3/10	30
NC	2/10	20
PD	5 /10	50
Overall response rate (CR + PR) was 30 percent.		

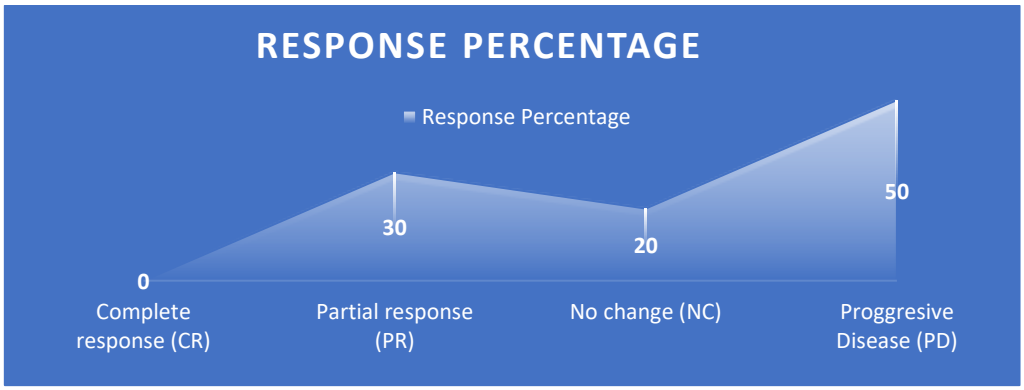

Fig.6: Miscellaneous group cancer response percentage curve

Overall objective response:

The overall objective response varied across different cancer types, with colorectal cancer displaying a poor response rate of 20%, miscellaneous cancers at 30%, and gastric, gall bladder, and stomach cancers showing more favorable response rates at 40% and 50% respectively. Refer to Table 7 for a breakdown of the overall objective response among various cancer groups.

c. Subjective Response:

Subjective response was gauged by changes in performance status. Notably, improvements in performance status (at least 1 WHO grade) were observed in 5 out of 10 (50%) cases of stomach cancer, 4 out of 10 (40%) cases of gall bladder cancer, and 3 out of 10 (30%) cases in the miscellaneous cancer group. In contrast, only 2 out of 10 (20%) cases of colorectal cancer showed enhancements in performance status. Refer to Table 8 for detailed information on changes in performance status across different cancer types.

d. Toxicity: (Table-9)

I. Gastrointestinal: Nausea/ vomiting was well controlled by anti-emetic therapy given concurrently with anticancer drugs (Metoclopramide, 10 mg IV at 0, 12 and 18 hours on day 1). Transient nausea occurred in 12/40 (30 percent) of patients treated and lasted for 1-2 days. 7/40 (17.5 percent) patients experienced transient vomiting (days 1 and 2) which was controlled by oral administration of Metoclopramide. Stomatitis occurred in 8/40 (grade-1) cases constituting 17 percent of the treated cases. Diarrhoea occurred in 2/40 (5 percent) cases and was transient (grade-1).

II. Haematologic: Total leucocyte and platelet counts became depressed after chemotherapy, and nadir values of leucocytes and platelets were reached in the second-week post therapy. In all cases, counts reached normal values at week 4.

Nadir's total leucocyte values were as follows:

Value (x 1000 cells/mm^3)	Percentage of patients
4.0 or more	40
3.0 – 3.9	42
2.0 – 2.9	18
1.0 - 1.9	-
Less than 1.0	-

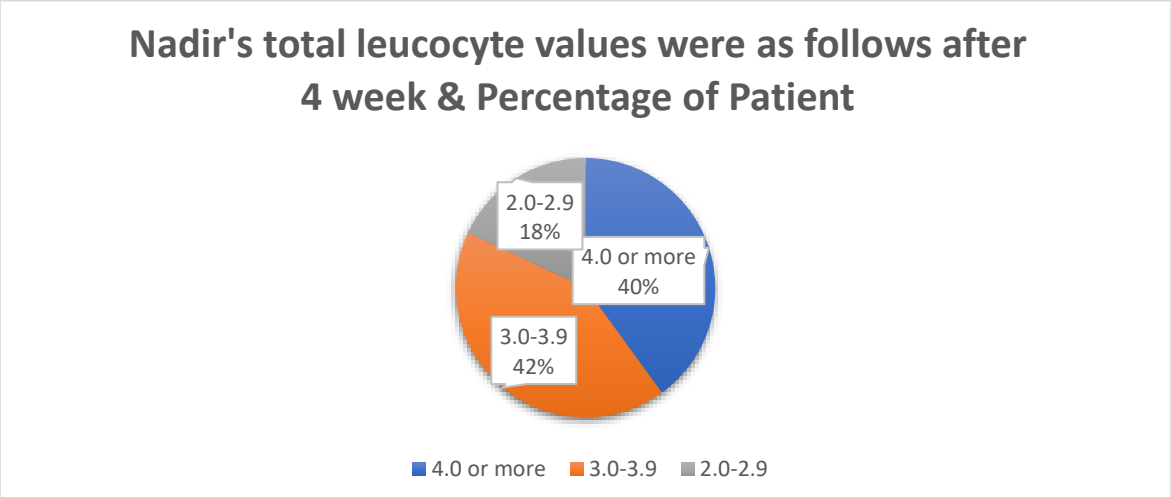

Fig. 7 : Pie Chart representing percentage of Nadir's total leucocyte values

Nadir platelet Values:

Platelate Count (x 1000/mm^3)	Percentage of Patients
100 or more	44
75 - 99	32
50 - 74	24
25 - 49	-
Less than 25	-

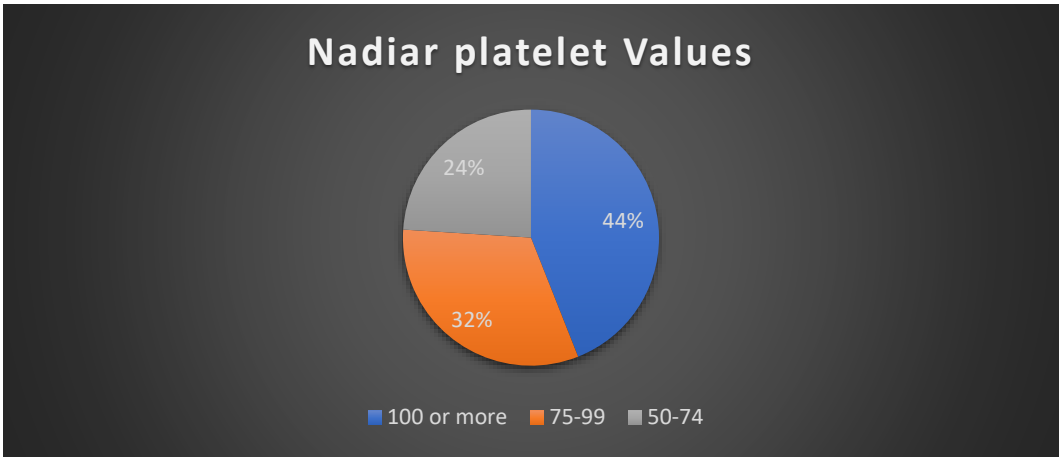

Fig. 8 : Pie Chart representing percentage of Nadir's Platelet values

None of the patients experienced an episode of infection or thrombocytopenic haemorrhage secondary to the bone marrow depression.

III. Alopecia- occurred in 3/40 (7.5 percent) patients, who could be followed for 2 cycles of chemotherapy. Minimal hair loss occurred in 2 patients, in the other 1 there was moderate patchy alopecia.

IV. Renal toxicity- was not observed in any patient.

PHA skin response:

The PHA skin response, measured as millimeters of induration occurring 24 hours following 10 ug of PHA intra- dermally has been presented in Table 10.

The mean pretreatment PHA skin response in cancer patients varied from 7.4 to 9.0 mm which was significantly lower than the control value of 18.4 mm. PHA skin response, measured at 6-week post therapy improved in patients achieving complete or partial response while it did not change in non-responders.

Pre-treatment PHA response did not significantly differ in the responders and non-responders.

Follow-up studies (Table 11)

Dropout was encountered in a large number of patients not responding to chemotherapy. Out of 26 patients not showing any objective response to chemotherapy only 5 could be followed up to 12 weeks. Enquiries by letters sent at the patient's address revealed that 26/26 (100 percent) of these patients were dead by 14 weeks. The median survival after chemotherapy was 8.2 weeks in patients not responding to chemotherapy.

Out of 5 responders (2 CR + 3 PR) from the stomach cancer group, 1 patient had attained CR survival for 27 weeks, while others lived for 10, 12, 14, and 15 weeks respectively. Mean survival was 15.6 weeks.

Out of 4 responders (1 CR + 3 PR) from the gall bladder cancer group, the patient who attained CR is still alive, (survival 25 weeks) and is ambulant (Performance status grade-2). Four patients who had achieved

PR lived for 8,11,14 and 15 weeks respectively.
The only responder (PR) in the colorectal cancer group is still in remission 12 weeks after start of therapy.

Table-4: Showing age and sex distribution of patients.

Diagnosis	Number of Patients	Age in years	
		Mean ± 1 S.D.	Range
Cancer Population*			
Stomach Cancer	10	58.6 ± 12	45 - 66
Gall bladder Cancer	10	48.2 ± 10.6	36 - 58
Colorectal Cancer	10	56.6 ± 13.4	47 - 62
Miscellaneous	10	59.6 ± 10.4	48- 68
Control Population	20	54.4 ± 12.8	46 - 66

*Patients Grouped according the primary tumour site.

Table-5: Showing distribution of measurable lesions and performance status.

Diagnosis	Number of Patients	Measurable tumour lesion's			Performance Status Grade (Number and Percentage)				
		Liver	Abdominal mass	Peripheral lymph node	Grade -0	Grade -1	Grade -2	Grade -3	Grade -4
Metastatic cancer									
From Stomach	10	9	8	6	0	0	**5** (41.6%)	3 (25%)	4 (33.2%)
From Gall Bladder	10	8	7	6	0	0	**5** (33.3%)	**2** (16.6%)	6 (50.00%)
From Colorectal Site	10	8	0	2	0	2 (20%)	2 (20%)	2 (20%)	4 (40%)
From Miscellaneous Primary	10	8	2	5	0	1 (9.0%)	2 (18%)	5 (45.4%)	3 (27.2%)
TOTAL	40	33	17	19	0	3	13	12	17

Table-6: Showing Details of patients dying during the first 4 weeks after therapy.

SL. NO	Primary	Pretherapy Performance Status	Haematologic Toxicity			Biochemical Values			
			Nadir TLC	Nadir Platelet	Complication	Serum Bilirubin		Serum Creatine	
						Pretherapy	Before Death	Pretherapy	Before Death

	tumour Site								
1	Stomach	4	2200	60,000	None	10.8 mg%	4.4mg %	0.8 mg%	3.6mg %
2	Colon	4	2600	8,000	None	3.2 mg%	3.4mg %	1.4 mg%	1.2mg %
3	Rectum	4	2300	70,000	None	4.8 mg%	6.0mg %	1.1mg%	1.4mg %
4	Gall Bladder	4	2700	60,000	None	24.0 mg%	18mg %	1.5mg%	1.8mg %
5	Breast	4	2300	50,000	None	6.0 mg%	7.0mg %	1.2mg%	1.0mg %
6	Breast	4	2100	80,000	None	2.0mg%	4.0mg %	0.8mg%	0.7mg %

Table 7: Objective tumour response

Primary tumour	No. of Patients treated	Deaths* during therapy	Patients evaluable for response	Tumour Response			
				CR	PR	NC	PD
Carcinoma Stomach	10	2	8	2/10(20%)	3/10(30%)	4/10(40%)	1/10(10%)
Carcinoma gall bladder	10	1	9	1/10(%)	3/10(30%)	4/10(40%)	2/10(20%)
Colorectal Carcinoma	10	2	8	0/10	2/10(20%)	5/10(50%)	3/10(30%)
Miscellaneous	10	2	8	0/10	3/10(30%)	2/10(20%)	5/10(50%)

*These patients died of cause not related to therapy. All of these deaths occurred during first cycle of Chemotherapy.

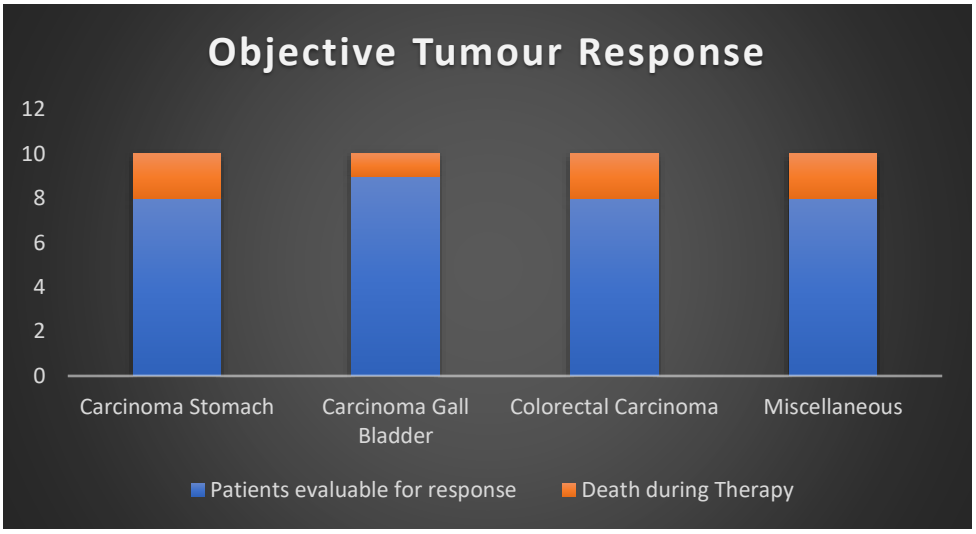

Fig.7: Column Chart representing objective tumour response

Table 8: Showing improvement in performance status

(9 weeks after therapy)

Primary tumour site	No. of Patients evaluable*	No. of patients having improvement in performance status	Percentage of patients improving
Stomach	10	5	50
Gall bladder	10	4	40
Colorectal	10	2	20
Miscellaneous	10	3	30

*Patients dying of causes not related to therapy were not considered evaluable.

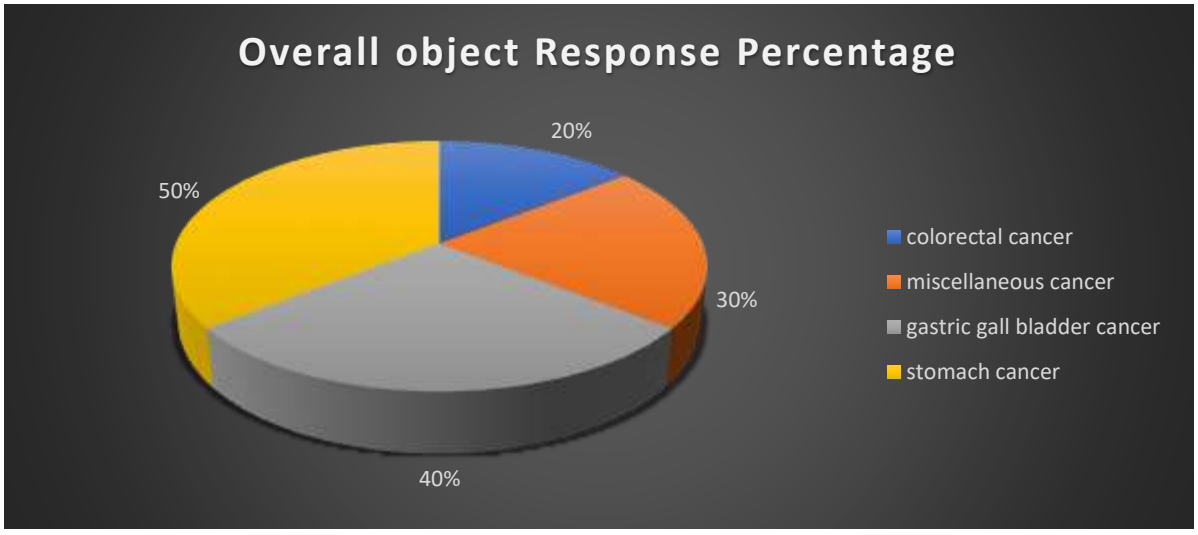

Fig.8: Overall objective response percentage chart

Table – 9: Showing distribution of toxicity following chemotherapy.

Toxicity grade	System affected					
	TLC nadir	Platlet nadir	Nausea/ Emesis	Stomatitis	Diarrhoea	Hair
0	40%	44%	18%	83%	96%	95
1	42%	32%	71%	17%	4%	2.5%
2	18%	24%	11%	0	0	2.5%
3	0	0	0	0	0	0
4	0	0	0	0	0	0

Table-10: Showing PHA skin test response.
(in mm of induration)

Primary tumour site	Values	Responders to chemotherapy (CR+PR)		Non-responders to chemotherapy (NC+PD)	
		Pretherapy	6 weeks after therapy	Pretherapy	6 week's after therapy
Stomach	Mean ±SD P	8.5 ± 4.3 .001	14.6 ± 3.2 .001	9.0 ± 3.8 .001	8.2 ± 2.6 N. S
Gall bladder	Mean ±SD P	7.8 ± 4.4 .001	13.8 ± 3.6 .001	7.4 ± 4.2 .001	8.9 ± 3.6 N. S
Colorectal	Mean ±SD P	8.0	13.0	7.9 ± 2.8 .001	6.8 ± 4.2 N. S
Miscellaneous	Mean ±SD P	8.4 ± 3.8 .001	13.2 ± 2.4 .001	7.9 ± 3.0 .001	7.3 ± 2.6 NS

PHA skin test response of control group= mean 18.4 ± 3.4
N.S.= Not significant
P value= Pretherapy value was calculated in comparison to control value and post therapy value was calculated in comparison to respective pretherapy values.

Table -11: Showing survival of patient with metastatic liver cancer.
(Only patients alive at 4 weeks were evaluated)

Chemotherapy responders (CR+PR) & Non responder (NC+PD)	Individual survival (in week's)	Mean survival (in weeks)
Chemotherapy responders (CR+PR)		
Primary tumour site:		
Stomach (5 Patients)	27, 15, 14, 12, 10	15.6
Gall bladder (4 patients)	>25, 15, 11, 8	>14.75
Colorectal (2 Patients)	12,18	15
Miscellaneous (3 Patients)	Not traceable after 8 weeks	8

Chemotherapy Non-responder's (NC+PD)		
25 patients	All dead by 14 weeks	14

DISCUSSION:

In this study, we conducted a comprehensive analysis of forty patients diagnosed with metastatic liver carcinoma, focusing on demographic parameters such as age and sex distribution, as well as the origins of primary tumors and their respective responses to combination chemotherapy. The investigation also explored the effects of chemotherapy-induced tumor regression on the in vivo evaluation of 'T' cell functionality, with particular emphasis on the phytohemagglutinin (PHA) skin test.

Additionally, our research aimed to assess the systemic toxicity associated with a brief course of combination chemotherapy, consisting of 5-fluorouracil (5-FU), cyclophosphamide, and mitomycin C, administered to individuals suffering from widely disseminated malignant conditions. For comparative analysis, a control group of twenty age- and gender-matched subjects, afflicted with non-inflammatory benign gastrointestinal disorders—comprised of ten cases of peptic ulcer and ten cases of cholelithiasis—was utilized for immunological assessment via the PHA skin test.

Recognizing the significant influence of age on immune system parameters, the control cohort was specifically selected to maintain age congruency with the cancer group. Furthermore, considering the impact of nutritional status on cellular immune responses, individuals exhibiting comparable nutritional profiles to those in the metastatic cancer group were chosen to serve as controls.

The liver is recognized as the primary site for metastatic neoplasms, predominantly originating from tumors in the gastrointestinal tract, mammary glands, and pulmonary structures. Post-mortem examinations indicate that over 50% of patients with gastrointestinal malignancies exhibit secondary hepatic involvement at the time of death.

In our investigation of 40 cases of histologically validated metastatic hepatic carcinoma, 25% of the tumors were derived from primary gastric carcinomas, another 25% from primary gallbladder neoplasms, and an additional 25% from colorectal origins. Mammary and ovarian tumors accounted for 12.5% and 5% of the liver metastasis cases, respectively, while the primary tumor site remained unidentified in 7.5% of cases. The elevated incidence of gastric and gallbladder carcinomas observed in our study contrasts with Western literature, which describes gallbladder cancer as comparatively rare in those populations.

The significant frequency of gallbladder cancer metastasizing to the liver identified in our research may be attributed to early hepatic dissemination and delayed clinical recognition, given the subtlety of this cancer during its initial stages, which often presents symptoms that mimic benign gallbladder conditions. A considerable number of these cases are diagnosed at an advanced stage and are classified as inoperable, with many exhibiting metastases to distal organs at the time of assessment. A prior institutional report indicated that 42% of patients with gallbladder cancer presented with hepatic metastases at presentation, while 55.5% demonstrated extensive local invasion by malignant processes. Only a marginal 2% of patients were viable candidates for curative surgical intervention. Our findings revealed that gallbladder cancer constituted 13% of biliary disorders, with gallstones present in merely 17% of gallbladder cancer patients.

Age and sex incidence:

Our study demonstrated that metastatic liver lesions originating from gastric, colorectal, and tumors of diverse origins (including undetermined primary, mammary, and ovarian) predominantly manifested during the sixth decade of life. This was in stark contrast to gallbladder malignancies, which

predominantly emerged in the first decade of life. The mean age of individuals exhibiting secondary hepatic deposits attributable to gallbladder cancer was recorded at 46 years.

Clearly, gallbladder cancer affects a significantly younger population within our cohort. Ethnic, socioeconomic, and dietary factors may potentially explain this unique pattern of gallbladder cancer incidence observed among our patients.

Parameters for assessment of response: Consistent criteria for evaluating chemotherapy response are essential for enabling comparisons across different studies. The present investigation adhered to the UICC guidelines for assessing objective tumor response based on histologically confirmed malignancies. Subjective improvement is equally important alongside tumor regression. The relationship between performance status and patient survival serves as a strong indicator of chemotherapy efficacy. In this analysis, changes in patient performance status were considered a subjective measure reflecting the response to anticancer treatment. A considerable proportion of our patient cohort exhibited delayed presentations and compromised overall health, as indicated by their reduced performance statuses. This trend appears to be specific to our study environment, likely influenced by socioeconomic factors and patient perceptions of their illnesses, which significantly contribute to the high prevalence of frail cancer patients in our population.

Combination chemotherapy:

The efficacy of single-agent chemotherapy in gastrointestinal and biliary cancers is limited. Over the past decade, combinations of two or more anticancer agents have been rigorously evaluated in an effort to enhance outcomes compared to single-agent therapies. Regrettably, this combination strategy has proven successful only in gastric cancer. Achieving effective palliation for other malignancies affecting the digestive system continues to pose a significant challenge in oncology..

Stomach cancer:

The combination of 5-FU and chloroethyl-nitrosourea has been extensively studied since the early 1970s. In our investigation, the administration of a regimen consisting of 5-FU, cyclophosphamide, and mitomycin-C yielded a combined complete and partial response rate of 50% in cases of metastatic gastric cancer. Among the patients who responded, one individual achieved a complete response and survived for 27 weeks, while other responders had survival times ranging from 10 to 15 weeks. The average survival duration for responders was found to be 15.6 weeks, which is significantly higher than the average survival of 8.2 weeks noted in non-responders across all cancer categories.

Colorectal cancer:

The effectiveness of combinations involving 5-FU with chloroethyl nitrosourea or three-drug regimens has not been demonstrated in colorectal cancer, as noted by Haskel in 1980. As a result, 5-FU monotherapy continues to be the standard treatment option, as emphasized by Monfardini *et al* . in 1981.

Our research findings are consistent with these foundational studies. When we administered the combination of 5-FU, cyclophosphamide, and mitomycin-C to colorectal cancer patients, we observed a modest objective response rate of only 20%, with a significant 75% of patients experiencing disease progression despite receiving chemotherapy. This response rate is notably lower than the 50% and 40% response rates observed in cases of gastric and gallbladder cancers, highlighting the inferior treatment outcomes in colorectal cancer.

Gall bladder cancer:

In our study, we observed a total of five responses—including one complete response and three partial responses—among eleven patients with gallbladder carcinoma that had metastasized to the liver, resulting

in a response rate of 40%. The patient who achieved a complete response remained in remission for 25 weeks after starting therapy and demonstrated a marked improvement in overall well-being, with a performance status improvement from grade 4 to grade 2. Patients with partial responses had survival durations ranging from 8 to 15 weeks, with an average survival time of 12 weeks. In contrast, the average survival duration for metastatic liver cancer patients who did not respond to the treatment (across all cases) was only 8.2 weeks.

Drug toxicity:

In our treatment protocol, 5-FU was administered at a dosage of 1000 mg/m² intravenously at 0 hours on day 1, followed by cyclophosphamide at 600 mg/m² intravenously at 12 hours on the same day, and mitomycin-C at 10 mg/m² intravenously at the 18th hour on day 1. This cycle was repeated after a four-week interval. Additionally, metoclopramide was given intravenously at a dosage of 10 mg at 0, 12, and 18 hours alongside the anticancer agents.

Overall, this treatment regimen was well tolerated, with only mild bone marrow depression observed. The lowest total leukocyte count (TLC) and platelet counts were recorded in the second week, followed by a complete recovery of hematological parameters by the fourth week. Approximately 42% of cases experienced a TLC nadir ranging between 3000 and 4000 cells/mm³, while TLC values below 3000 and 2000 were observed in 18% of cases. Importantly, none of the treated patients exhibited a TLC nadir beneath 2000 cells/mm³. In terms of platelet counts, a nadir ranging from 75,000 to 100,000/mm³ was noted in 32% of cases, with nadir counts below 75,000 and above 50,000 recorded in 24% of cases. Notably, none of the patients had nadir platelet counts below 50,000/mm³.

Nausea was not a significant concern, and transient vomiting was reported in only 30 patients. Our observations indicated significantly less leukopenia, with complete recovery of TLC by week 3 of chemotherapy, further supporting our findings regarding the tolerability of this regimen.

PHA skin response:

In patients with advanced gastrointestinal tract (GIT) cancers and other metastatic cancers, we observed a significant suppression of the PHA skin response. This reduced reactivity in the PHA skin test suggests a decline in cellular immune responsiveness and has been found to be a more effective measure than contact sensitizers like DNCB and recall antigens for assessing the competency of cellular immune function. It has been proposed as a reliable indicator of the operational efficiency of 'T' lymphocytes.

Our study specifically highlighted a marked decrease in PHA skin test responses among patients with secondary liver metastases, arising from tumors of the stomach, gallbladder, colorectal region, and other non-GIT organs. Notably, patients who demonstrated a favorable response to chemotherapy experienced a significant improvement in their PHA skin responses. In contrast, those who did not respond to chemotherapy showed no considerable change in their PHA skin reactivity. This finding underscores the potential relationship between chemotherapy responsiveness and the restoration of cellular immune function as measured by the PHA skin test.

The compromised cell-mediated immunity observed in patients with stage-4 cancers may stem from multiple factors, including tumor burden, malnutrition, recent extensive surgeries, or cancer treatments. However, the significant enhancement in cellular immune function, as indicated by improved PHA skin test responses, was exclusively noted in individuals who responded positively to therapy. This suggests that tumor mass and associated factors play a crucial role in immune suppression, highlighting the potential for reversibility of this condition.

Moreover, we observed a similar reversal of depressed PHA skin reactivity in patients with stage 1 and 2 GIT cancers following curative resection. This finding further supports the correlation between treatment response and immune competence in GIT cancer patients undergoing anti-cancer therapies. It underscores the importance of monitoring cellular immune function as a potential indicator of treatment efficacy and overall patient prognosis. Restoration of immune responsiveness may serve as an essential contributor to the success of cancer treatments, emphasizing the need for strategies aimed at enhancing immune function in these patients.

CONCLUSION:

Patients with metastatic liver carcinoma were examined through clinical, pathological, and immunological studies to evaluate their responses and side effects from short-term combination chemotherapy. Gallbladder cancer accounted for 26.6% of these cases, while a similar percentage originated from the stomach. Colorectal cancer represented only 22%, and 24.3% were due to breast, ovarian, or unidentified primary cancers. Metastatic gallbladder cancer typically occurred in patients in their 40s (average age 48.2), whereas other digestive cancers were more common in those in their 60s. The combination of 5-FU, cyclophosphamide, and mitomycin-C was generally well tolerated, with no severe bone marrow depression or complications related to low white or platelet counts; moreover, nausea and vomiting could be managed with metoclopramide. This chemotherapy led to objective tumor regression in 45% of advanced stomach and gallbladder cancer cases, though only 12.5% of colorectal cancer patients responded favorably. Complete responses were observed in 9% of advanced stomach and gallbladder cancer cases. Chemotherapy responders showed improved performance status and longer survival. Additionally, the PHA skin test responses were significantly lower in patients with metastatic liver deposits. Patients who achieved tumor regression improved their PHA response six weeks post-chemotherapy, while non-responders exhibited consistently low PHA responses. Initial PHA responses were similar between both groups before treatment.

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