

# Gall bladder cancer: India defines treatment for an Indian Cancer: GECOR-GB, RACE-GB & POLCA GB



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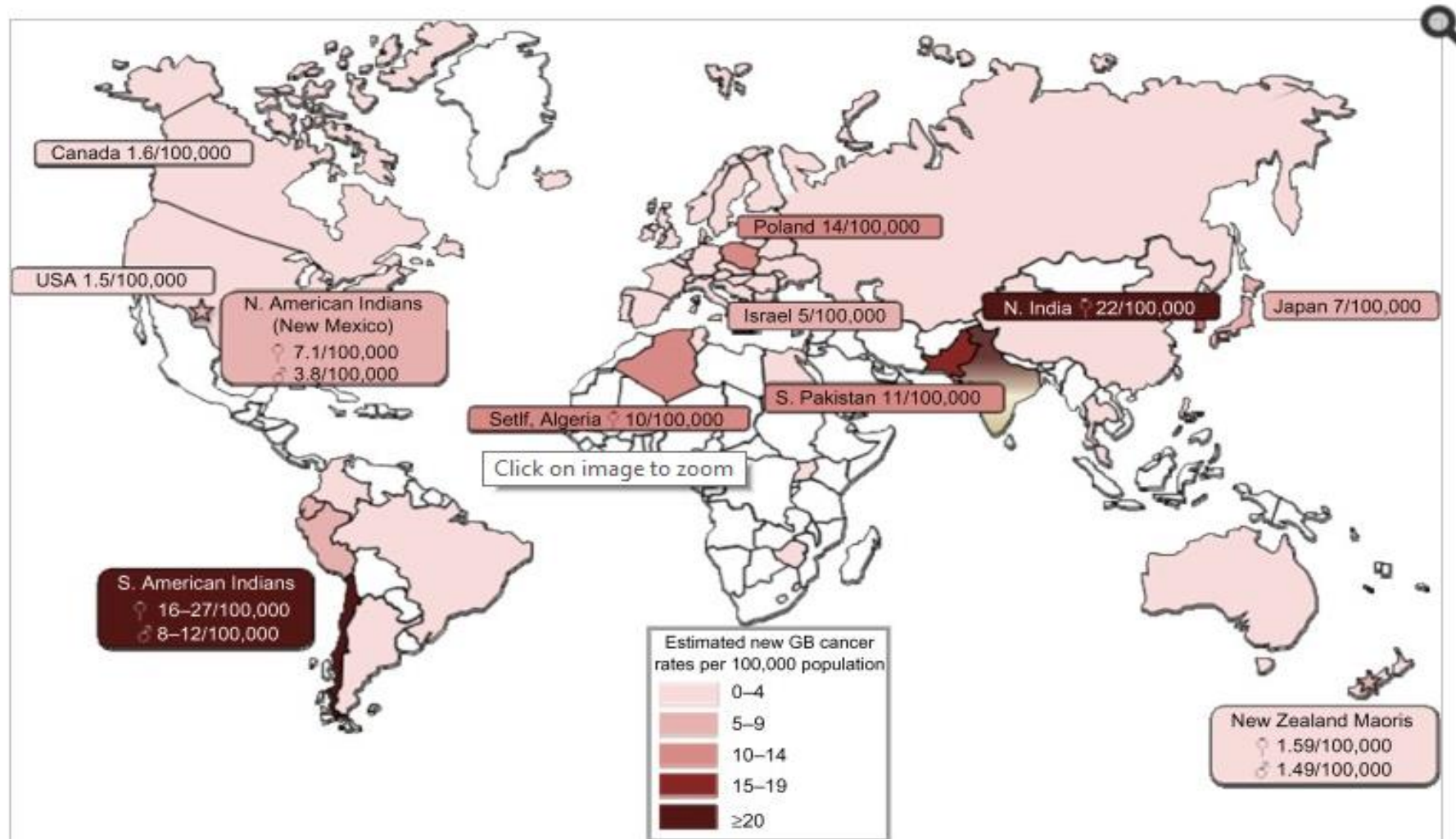
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Secretary, **GI Oncology Society**

Courtesy: Dr R. Engineer, Professor Radiation Oncology  
Gastro-intestinal Disease Management Group  
Department of Radiation Oncology, Tata Memorial Hospital, Mumbai

# GALLBLADDER CANCER

## “AN INDIAN DISEASE”

Figure 1



# INCIDENCE

- The incidence in North India is 10–22/100,000 population and is **similar to that of other countries with high incidence such as in South America** (Chile, Bolivia, Columbia).
- The incidence of **GBC in Delhi**, north India (4.1/100,000 men, 9.5/100,000 women), has been reported to be approximately **4-6 times higher compared with that in Bengaluru, South India** (1.4/100,000 men, 1.7/100,000 women)<sup>2</sup> .
- Recent projections estimate that by 2025, the number of patients with GBC in India will reach approximately **9.8 and 11.2 per cent among men and women**, respectively, across all patients worldwide .

# PATHOGENESIS OF GBC IN INDIA

- Multi-step process in which there is accumulation of genetic and epigenetic alterations due to host as well as environmental factors.
- **Obstruction** along the pathway for flow of bile due to CBD stone, stricture, sphincter of Oddi abnormalities can impede the emptying process.
- **Bacteria** once it enters the GB, is difficult for the body to eradicate.
- These bacteria tend to cause chronic inflammation, deconjugate conjugated bile acids and toxins and thus locally release toxic metabolites.
- **Chronic inflammation** results in mutagenesis especially of **the p-53 pathway** in India. Studies from India have shown that p53 mutations are detected in 70% (22).
- Patients with **GS more often have metaplasia and dysplasia** compared to those without GS.
- **Malnutrition** associated with micronutrient deficiency probably weakens the immune defenses which reduces immune surveillance for cancer

# RISK FACTORS FOR GBC

**Female Gender**

**>50 year**

**Geo-spatial epidemiology of gallbladder cancer in Bihar**

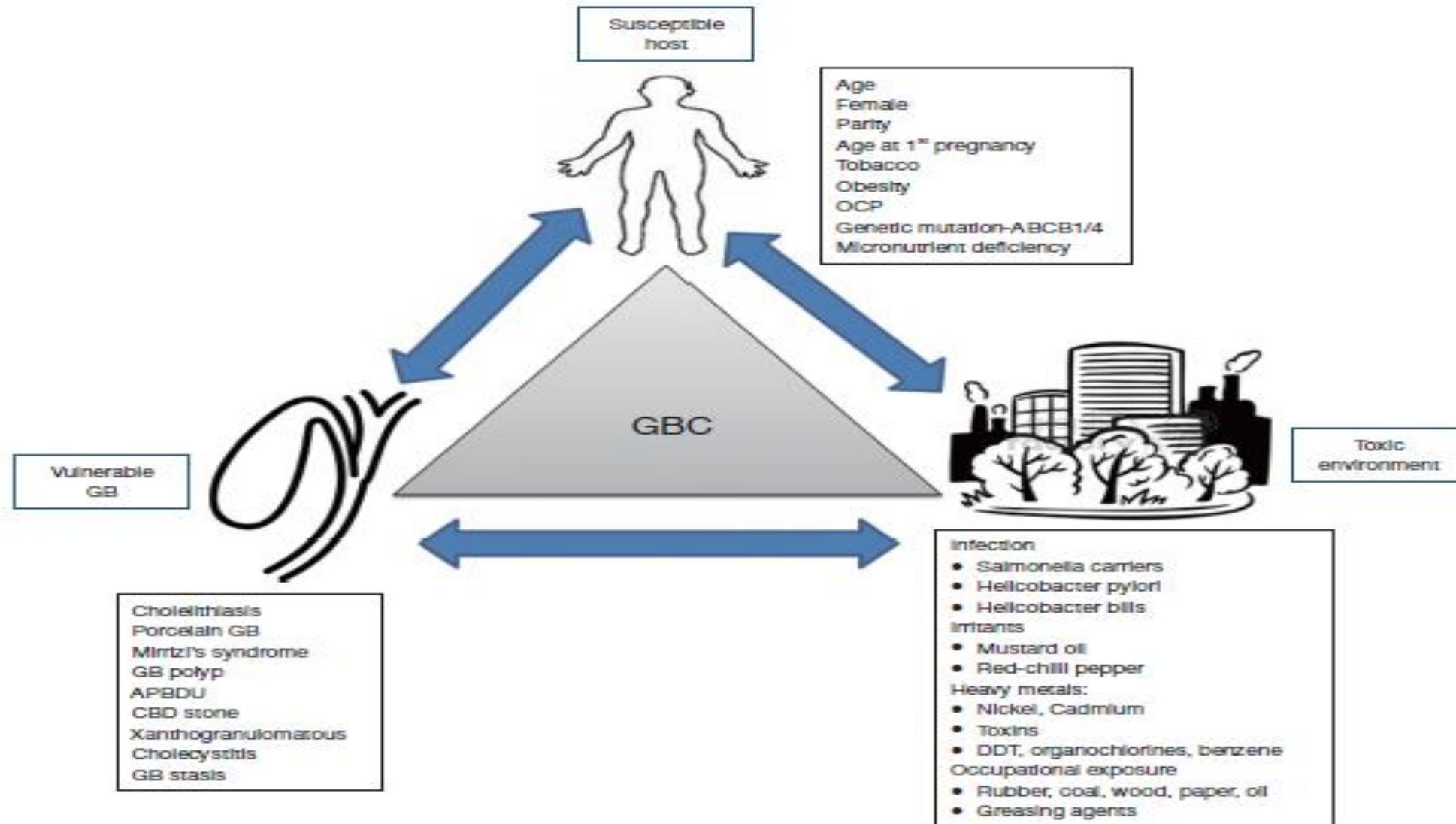
**Ethnicity, gender, age, gallstones, chronic inflammation, genetic factors ABCB1 and ABCB4 genes, CC genotype of the TP53 rs1042522 polymorphism**

**Gallbladder polyps**

## **Modifiable**

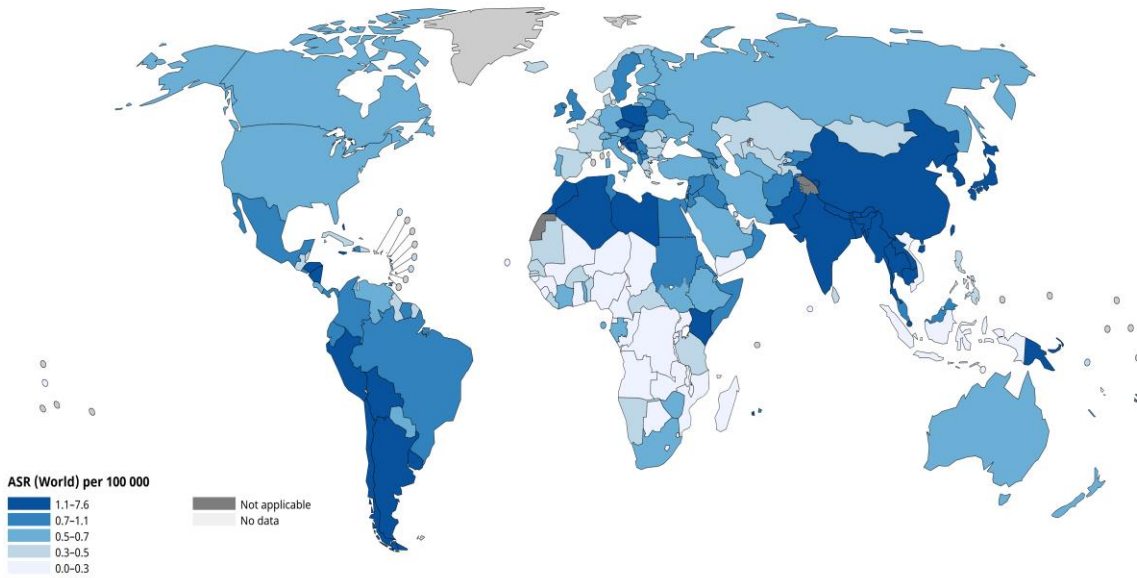
- Arsenic exposure
- Aflatoxin exposure
- H.Pylori
- Salmonella carriers
- Biomass fuel for cooking
- High consumption of mustard oil
- Low Vit D3 levels
- Lifestyle/Obesity/Diet

# RISK FACTORS FOR GBC



# Incidence

Age-Standardized Rate (World) per 100 000, Incidence, Both sexes, in 2022  
Gallbladder



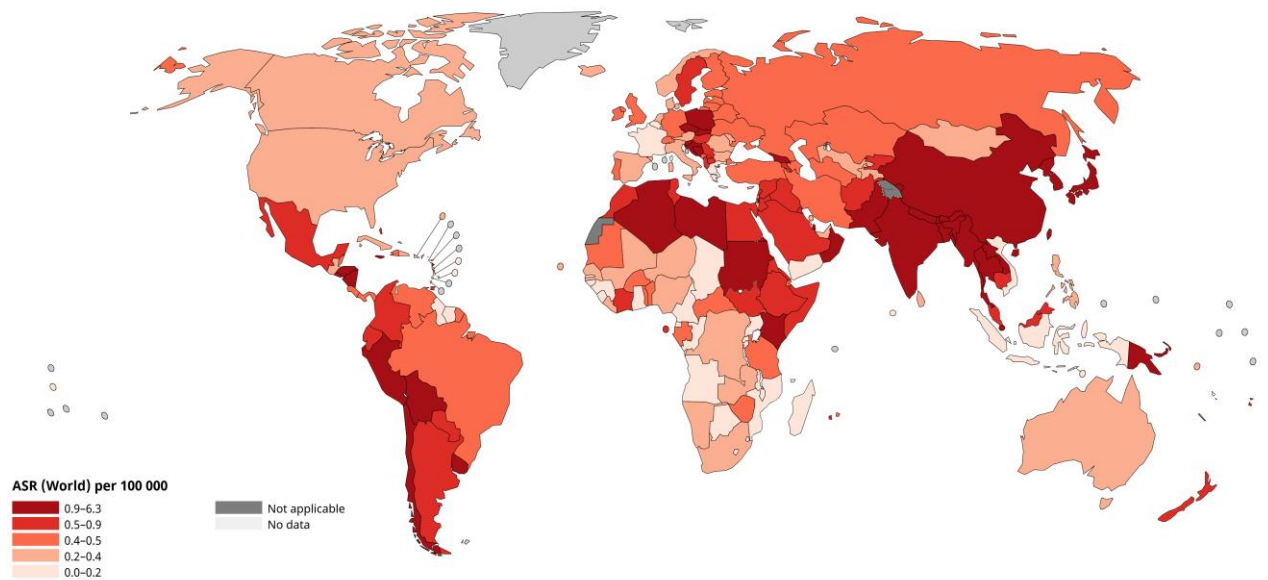
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Cancer TODAY | IARC  
<https://gco.iarc.who.int/today>  
Data version: Globocan 2022 (version 1.1) - 08.02.2024  
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# Mortality

Age-Standardized Rate (World) per 100 000, Mortality, Both sexes, in 2022  
Gallbladder



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Cancer TODAY | IARC  
<https://gco.iarc.who.int/today>  
Data version: Globocan 2022 (version 1.1) - 08.02.2024  
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Relatively rare – Outcomes are often clubbed with other BTC's !

# SX ALONE VS. POSTOP RT

## Evaluation of Adjuvant Radiation Therapy for Resected Gallbladder Carcinoma: A Multi-institutional Experience

**N=112**

**RT group had**

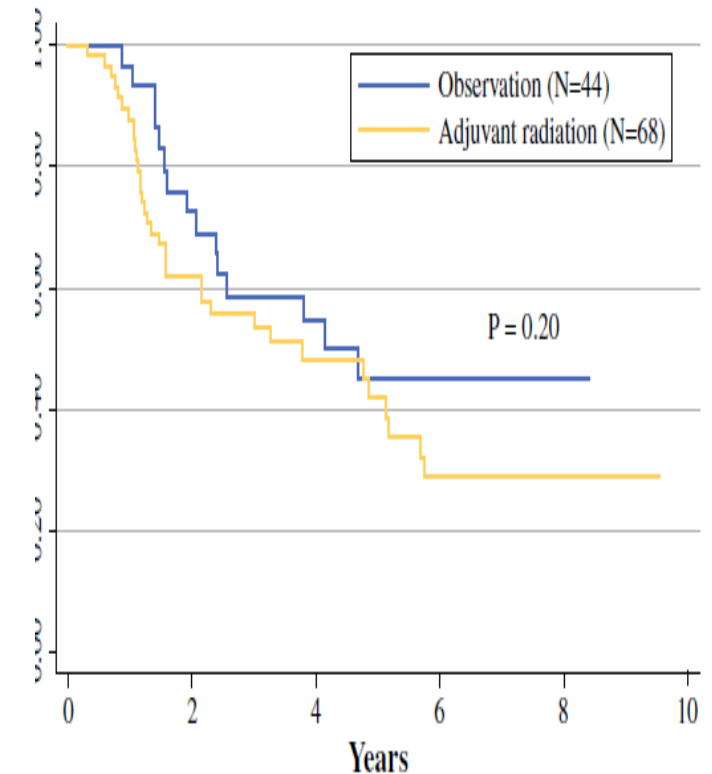
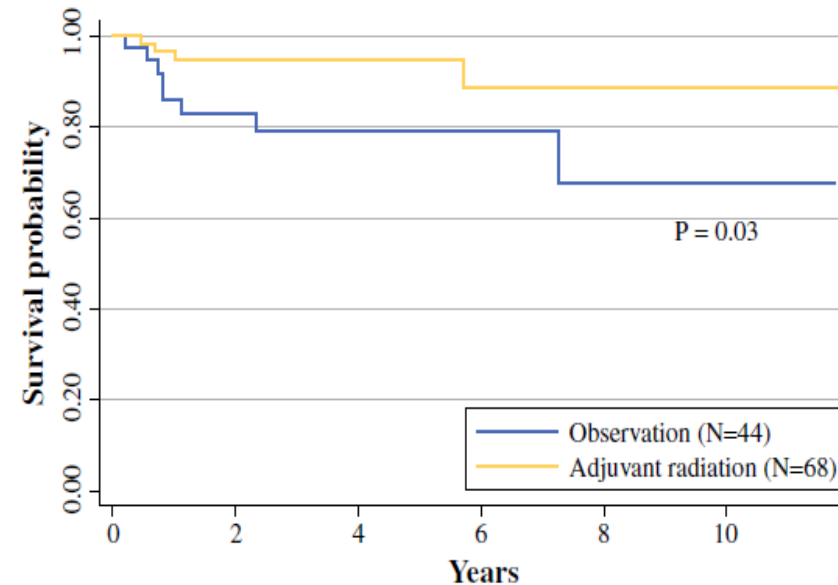
- Higher T-stage (57 vs. 16 %,  $p < 0.01$ )
- LN involvement (63 vs. 18 %,  $p < 0.01$ )
- +ve margins (37 vs. 9 %,  $p < 0.01$ )

**Adjuvant radiation**

**Decreased isolated local failure**

(HR 0.17, 95 % CI 0.05–0.63,  $p = 0.01$ )

71 % of recurrences included distant failure



**FIG. 2** Kaplan–Meier curves comparing time to isolated local failure between patients who received adjuvant radiation and those treated with surgery alone. Adjuvant therapy was significantly associated with a decreased time to isolated local failure

# ADJ CRT VS CT ALONE

## ADJUVANT THERAPY IN THE TREATMENT OF BILIARY TRACT CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

VOLUME 30 · NUMBER 16 · JUNE 1 2012

JOURNAL OF CLINICAL ONCOLOGY

20 studies - 6,712 patients 1960 – 2010

- Clear benefit with adjuvant therapy for high-risk patients
- Those receiving CT or CRT derived statistically greater benefit than RT alone (OR, 0.39, 0.61, and 0.98, respectively; *P* .02).
- The greatest benefit for AT was in those with LN-positive disease (OR, 0.49; *P* .004) and R1 disease (OR, 0.36; *P* .002).

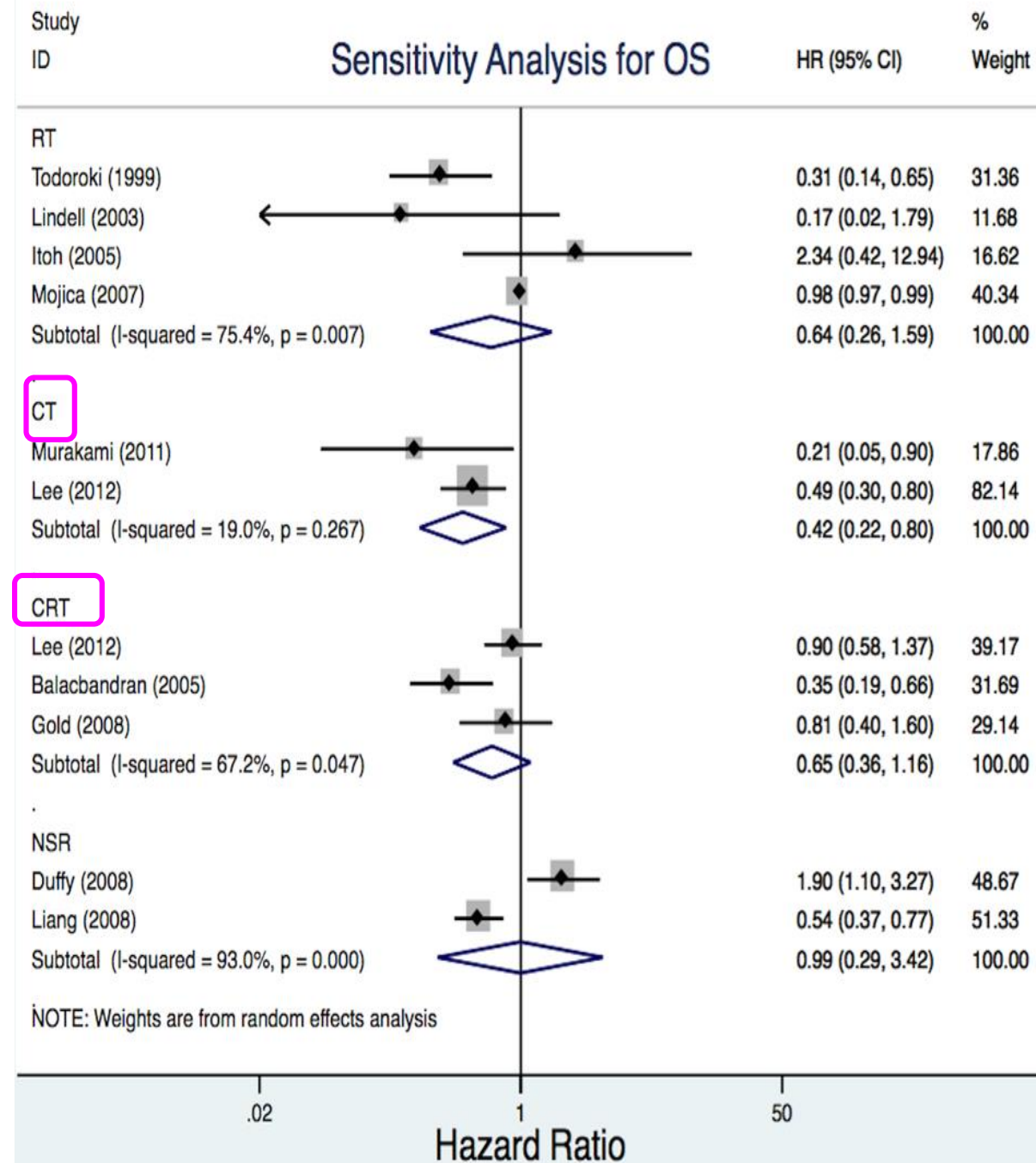
# META-ANALYSIS 2015

## MA ET AL

10 retrospective studies, -  
3,191 patients

Subgroup analysis – significant  
improvement in survival with  
CT (HR, 0.42; 95 % CI, 0.22–  
0.80) compared with surgery  
alone

Nonsignificant improvement in  
survival with RT and CRT.



# SWOG – 0809 – PATTERNS OF FAILURE

**Table 3.** Pattern of First Relapse

Recurrence	EHCC					
	Distal (n = 38)		Hilar (n = 13)		GBCA (n = 25)	
	No.	%	No.	%	No.	%
Local only	3	8	1	8	0	0
Local plus distant	5	13	2	15	2	8
Distant only	11	29	1	8	11	44
Total	19	50	4	31	13	52

Research

JAMA Oncology | **Brief Report**

# Adjuvant Gemcitabine Plus Cisplatin and Chemoradiation in Patients With Gallbladder Cancer A Randomized Clinical Trial

Vikas Ostwal, MD, DM; Shraddha Patkar, MCh; Reena Engineer, MD; Manali Parulekar, JNM;  
Sarika Mandavkar, JNM; Prabhat Bhargava, MD, DM; Sujay Srinivas, MD, DM; Rahul Krishnatry, MD;  
Shivakumar Gudi, MD; Akhil Kapoor, MD, DM; Durgatosh Pandey, MCh; Swapnil Patel, MCh; Abhishek Singhal, MD;  
Alok Goel, MD, DM; Tapas Kumar Dora, MD, DM; Debashish Chaudhary, MCh; Deepali Chaugule, MSc;  
Deepali Naughane, BDS; Anuprita Daddi, MD; Rajshree Patil, BSc; Suman Kumar Ankathi, MD;  
Anant Ramaswamy, MD, DM; Mahesh Goel, MCh

Figure 1. CONSORT Diagram

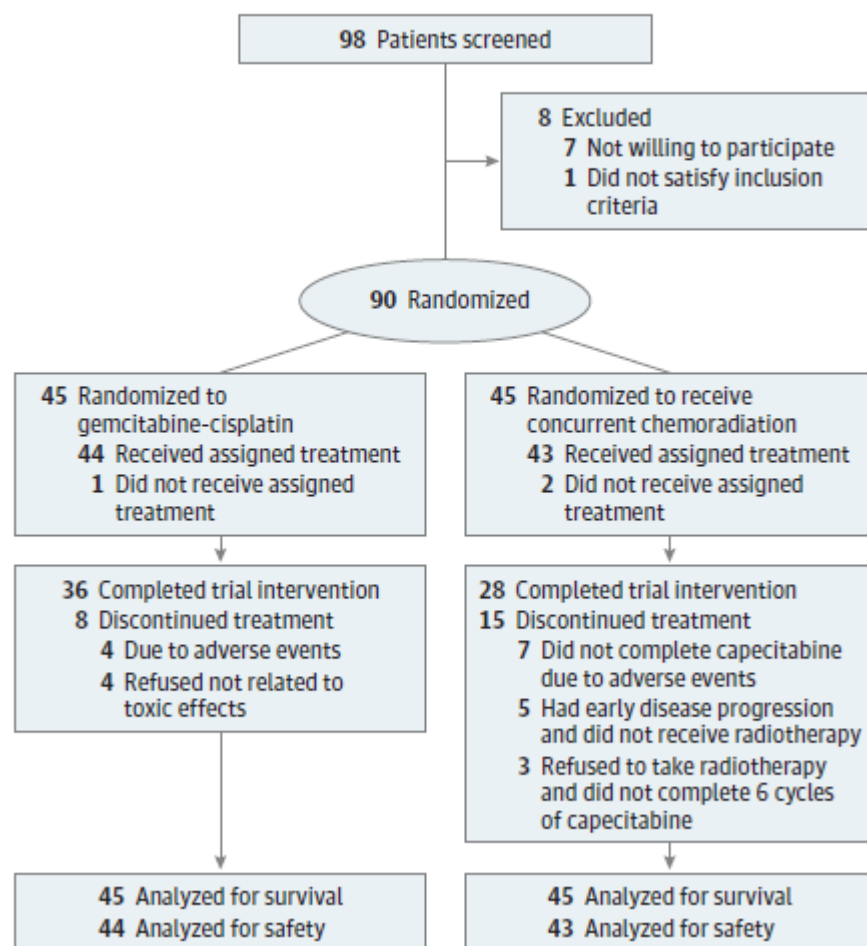
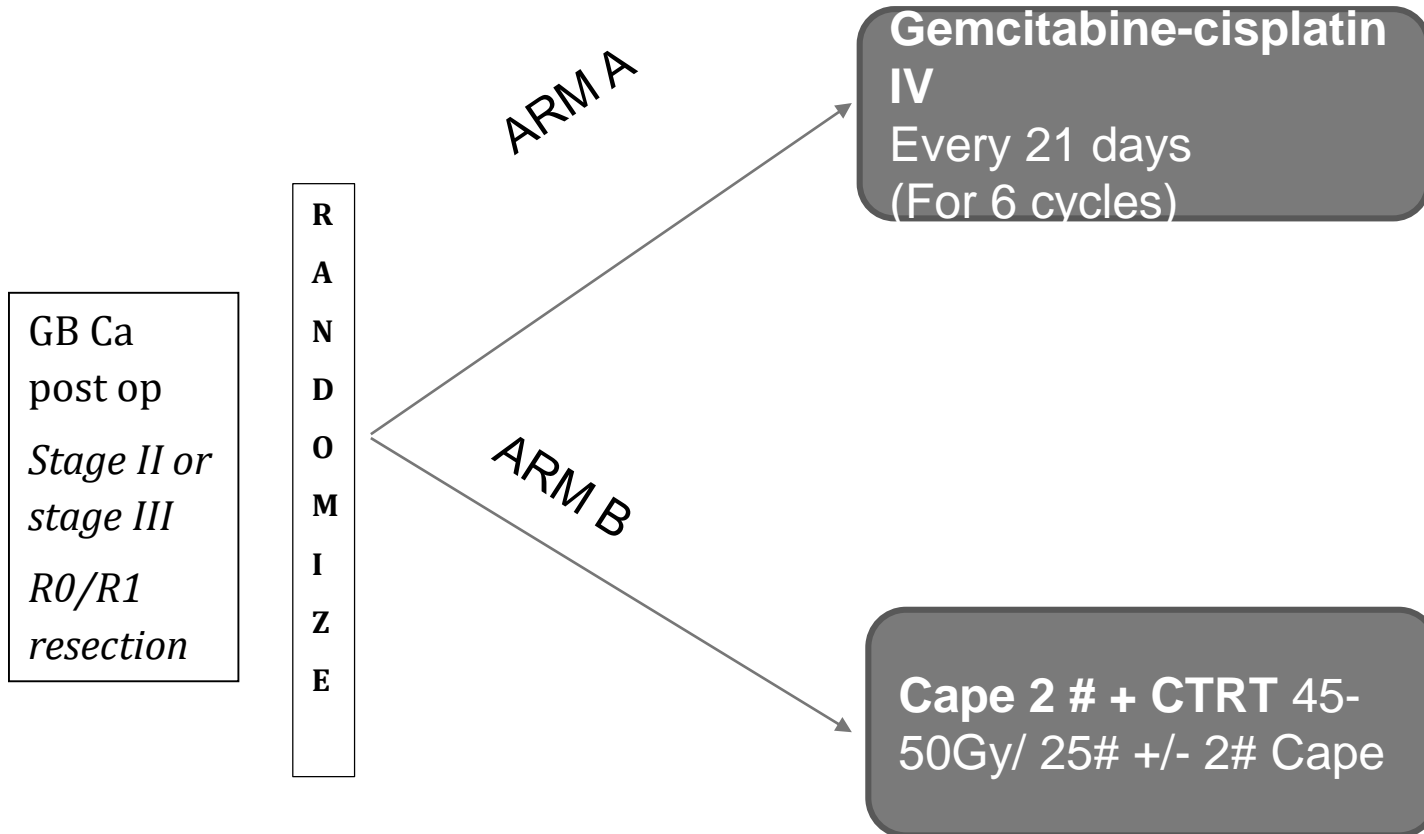


Table. Baseline Characteristics (Intention-to-Treat Population)

Variable	No. (%)	
	Gemcitabine plus cisplatin (n = 45)	Concurrent chemoradiation (n = 45)
Age, median (range), y	56 (33-72)	55 (26-69)
Sex		
Female	31 (69)	34 (76)
Male	14 (31)	11 (24)
T stage		
T1	1 (2)	0
T2	33 (73)	35 (78)
T3	11 (24)	10 (22)
Lymph node stage		
N0	28 (62)	32 (71)
N1	17 (38)	13 (29)
Staging		
Stage II	23 (51)	27 (60)
Stage III	22 (49)	18 (40)
Histologic findings		
Well differentiated	5 (11)	3 (7)
Moderately differentiated	32 (71)	35 (78)
Poorly differentiated	5 (11)	7 (16)
Not specified	3 (7)	0
Time to randomization, median (IQR), d	21(17-21)	22 (15-22)
Surgery		
Simple cholecystectomy followed by revision surgery	25 (56)	20 (44)
Radical cholecystectomy	20 (44)	25 (56)
Lymph nodes removed	11 (1-35)	12 (0-25)
Resection status		
R0	45 (100)	41 (91)
R1	0	4 (9)

# A TWO ARM RCT OPEN LABEL PHASE II CLINICAL TRIAL – GEMCITABINE-CISPLATIN OR CAPECITABINE AND CONCURRENT CHEMORADIATION IN OPERATED STAGE II & III GB CANCER (GECCOR-GB)



## Endpoints/Outcomes

- 1 year DFS (Primary endpoint)
- OS
- Quality of life
- Tolerance
- Toxicity
- Completion rates

# RESULTS – 3 YEARS UPDATED RESULTS

The 3-year DFS was 54.3% in the GC arm and 70.7% in the Cape-RT arm, respectively. The 3-year OS was 75% in the GC arm and 73% in the Cape-RT arm, respectively. The 3-year OS in stage II patients (n = 23) in the GC arm was 91.3%, while in the cape-RT arm (n = 27), it was 91.9%. Median OS in stage III patients (n = 22) was 39.1 (95% CI, 33.4–44.6) months in the GC arm, while in the cape-RT (n = 18), it was 23.2 (95% CI, 7.0–39.4) months.

# **SUMMARY – RESECTABLE GBCA**

**For T2+ GB cancers undergoing R0 resection**

**Adjuvant RT is superior to Sx alone**

**Adjuvant CRT is superior to RT alone**

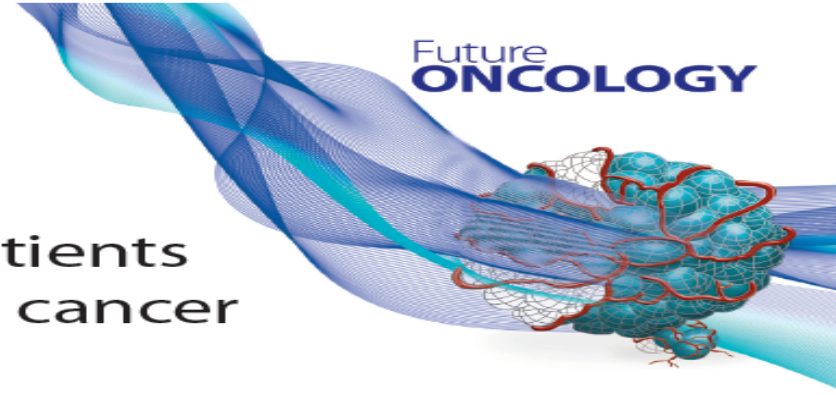
**Adjuvant CRT vs. CT alone - Combination of CT and CRT (Sequenced treatment) should be the current standard of care**

## RESEARCH ARTICLE

# Neoadjuvant chemotherapy in patients with locally advanced gallbladder cancer

Bhawna Sirohi<sup>\*1</sup>, Abhishek Mitra<sup>2</sup>, Palepu Jagannath<sup>3</sup>, Ashish Singh<sup>1</sup>, Mukta Ramadvar<sup>4</sup>, Suyash Kulkarni<sup>5</sup>, Mahesh Goel<sup>2</sup> & Shailesh V Shrikhande<sup>2</sup>

Future  
**ONCOLOGY**



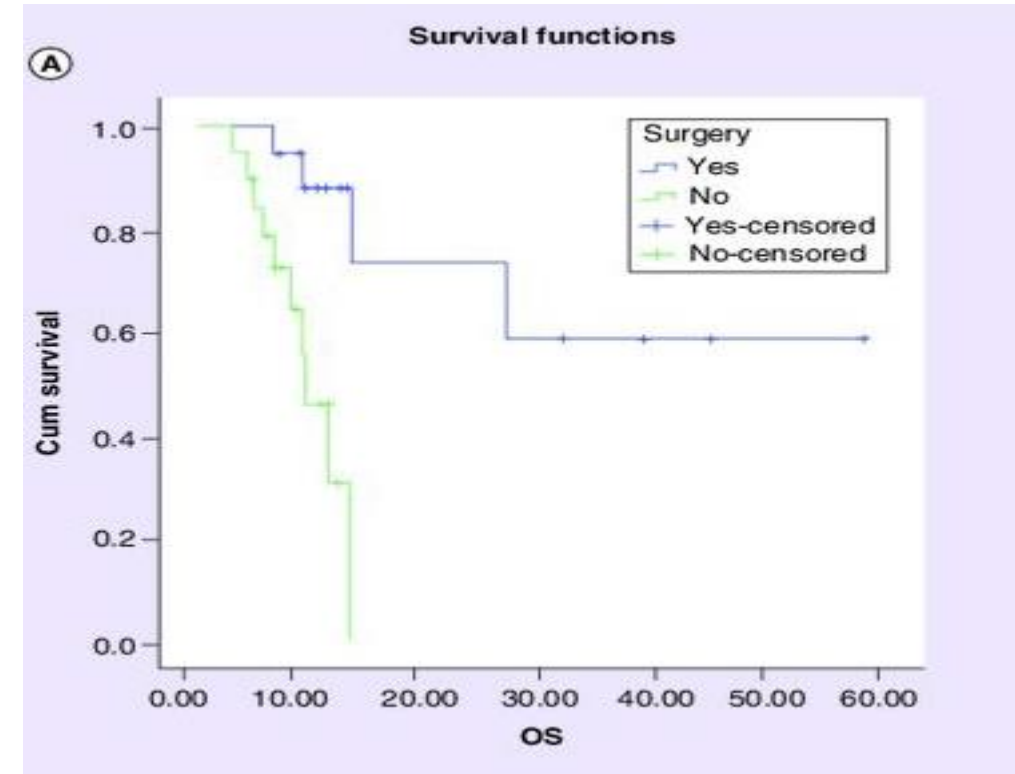
37 patients

67 % Overall response rate

46 % (n=17) underwent R0 resection

Median OS 13.4 months, PFS 8.1 months

Patient undergoing R0 surgical resection had better OS and PFS



# LOCALLY ADVANCED GBC

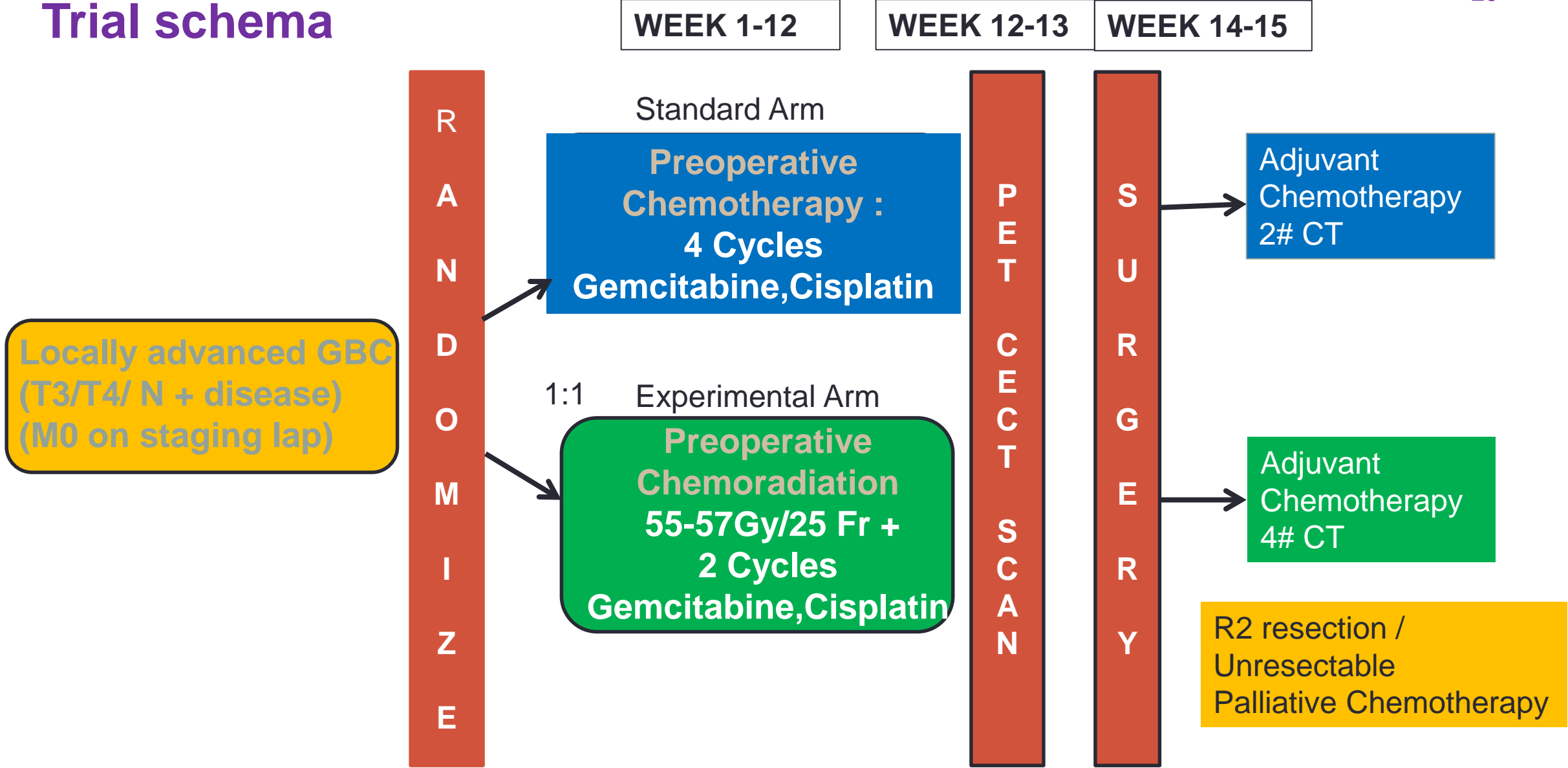
- Gall bladder cancers - majority present in locally advanced, inoperable, or metastatic stages
- R0 surgical resection is the only curative treatment
- Locally advanced high risk borderline resectable tumors undergoing aggressive multi-organ resections – poor outcomes (5year OAS<15%) – futile surgeries (Serenari 2025, Patel 2022)
- Tumors not amenable for R0 resection are often treated by Neoadjuvant chemotherapy leading to R0 resection rates of <40% and long term survival of <15%
- Role of Neoadjuvant Chemoradiation is not well defined

# Neoadjuvant chemotherapy or chemoradiotherapy in locally advanced gallbladder cancer

The POLCA-GB Trial (NCT02867865)

**R.Engineer**, M.Goel, V.Ostwal, S.Patkar, S.Gudi, A Ramaswamy, S.Kannan, N.Shetty, K.Gala, A Agarwal, M.Ramadwar, P.Patil, S.Mehta, R.Krishnatry, S.Pradhan, L.Pujari, S.Chopra, D. Chourasiya, S.Gupta

# Trial schema



# Main Eligibility Criteria

## Inclusion Criteria

- Histology: Adenocarcinoma
- Stage III gallbladder adenocarcinoma (AJCC 7th edition)

### **T3 or T4 tumors having**

- ✓ Liver >2 cm to <5 cm direct liver infiltration  
or
- ✓ vascular involvement of key hepatic blood vessels of less than 180 degrees.
- Lymph node involvement up to the N1 stage,
- Obstructive jaundice without hepatic hilar involvement as well as serosal invasion of the adjacent bowel.

## Exclusion Criteria

- Squamous or other non adenocarcinoma histology
- Clinical Stage 1&2
- Type 2 hilar non communicating block
- Patients with mucosal bowel involvement confirmed by endoscopy
- Any evidence of distant metastasis

# Endpoints

## Primary

- Overall survival between the two groups

## Secondary

- EFS
- R0 surgical resection rate
- Acute and late toxicities
- Postoperative complications
- Quality of life (QOL) between two study arms

# Sample size and Accrual

Median OS (Primary endpoint)

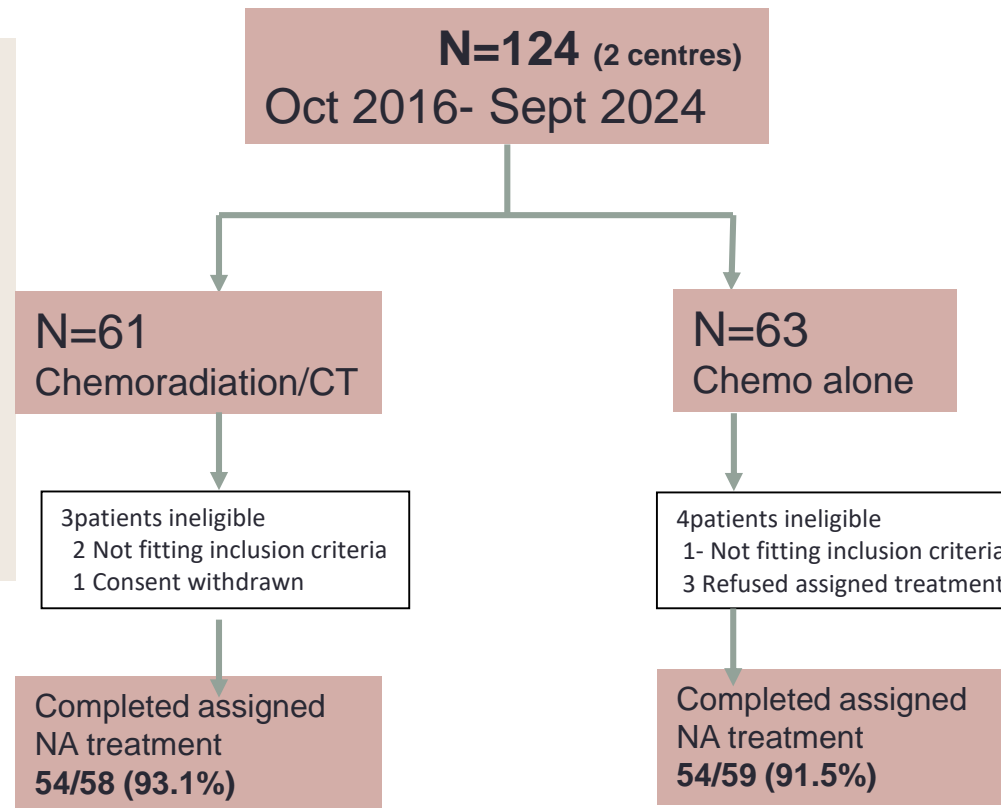
11 months (Standard Arm)



16.5 months (Experimental Arm)

N= 314 patients – 5 Years

(HR, 0.7; 2-sided  $\alpha = 0.05$ ;  $\beta = 0.2$ )



## The robustness of the interim analysis

Controlling for potential type I error inflation

Post-hoc evaluation was performed using the Hwang, Shi, and DeCani alpha spending function method, adjusted for a single interim analysis

# Characteristics of Trial Patients

<b>Characteristic</b>	<b>Chemoradiation Group N=61</b>	<b>Chemotherapy Group N=63</b>
Median age (range) — year	51 (45-61)	53.50(47-58)
Female	62.3%	66.7%
ECOG >0	78.7%	82.6%
Stage AJCC		
Stage IIIA	19.7%	22.2%
Stage IIIB	55.7%	68.3%
Stage IVA	<b>24.6%</b>	<b>9.5%</b>
Jaundice requiring External Drainage	26.2%	25.4%
Liver infiltration		
Absent	32.8%	27%
<2cm	9.8%	11.1%
>2cm	57.4%	61.9%

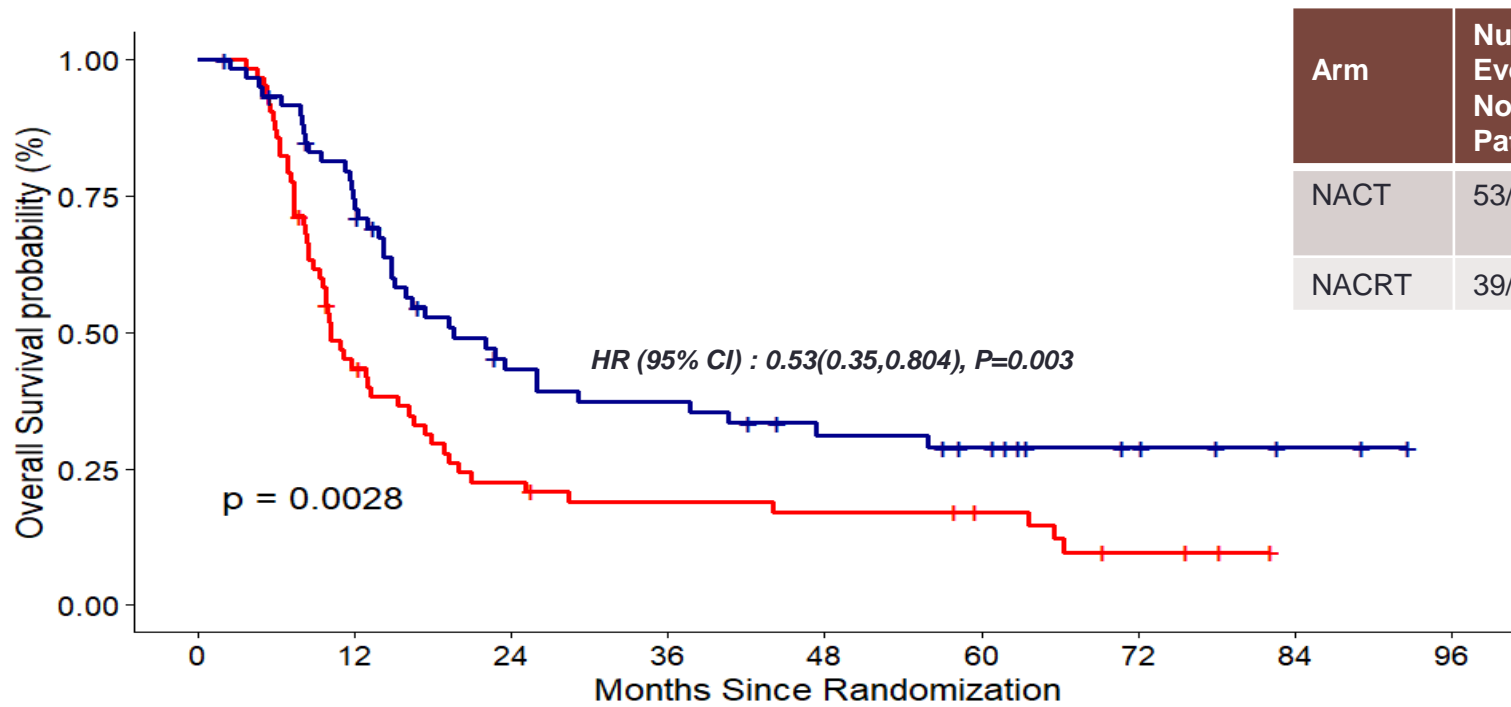
# Response (RECIST) to NAT (PET-CECT)

	Chemoradiotherapy (N=58)	Chemotherapy (N=59)	p
<b>Overall response rate (CR+PR)</b>	<b>43 (74.1%)</b>	<b>(35.5%)</b>	<b>0.001</b>
<b>Complete Response</b>	<b>25(43.1%)</b>	<b>6(10.2%)</b>	
Partial Response	16(27.6%)	14(23.7%)	
Stable Disease	2(3.4%)	11(18.6%)	
<b>Progressive Disease/Inoperable</b>	<b>12(20.7%)</b>	<b>26(44.1%)</b>	
Not assessed	3(5.1%) 1- Died during NAT of cholangitis 1- Road accident 1- Suicide	2(3.4%) Took 2 # due to G3 toxicity of chemo then defaulted	

# Surgical Details

	Chemoradiotherapy (N=58)	Chemotherapy (N=59)	p
<b>S Surgical exploration</b>	<b>38 (65%)</b>	<b>27 (45.7%)</b>	0.02
Reasons not explored	14- Disease Progression 1- Refused Surgery 2- Medically inoperable 3- Not assessed	27 – Disease Progression 2- Toxicity of NACT 3- Medically inoperable	
<b>R0 Resection</b>	<b>32/38(84.2%)</b>	<b>19/27 (70.3%)</b>	
R1 Resection	0	2(7.4%)	
R2 Resection	1(3.1%)	1(3.7%)	
Metastatic disease at exploration	5(13.1%)	5(18.5%)	
Adjuvant chemotherapy	27/32(84.3%)	19/21 (90.4%)	

# Overall Survival - ITT Population



Arm	Number of Events/ No. of Patients	Median survival(95% CI) Months	5-Y Survival (95% CI)
NACT	53/63	10.15(8.087,12.217)	17 (9-30)%
NACRT	39/61	21.8(14.79,28.967)	28.9 (18.9 – 44.6)%

Median follow-up - 62 months

Number at risk

	0	12	24	36	48	60	72	84	96
NACT	63	26	13	10	9	7	3	0	0
NACRT	61	42	22	19	14	11	5	2	0

# Postoperative Complications- Surgery Population

Clavien–Dindo	Chemoradiotherapy (N=38)	Chemotherapy (N=27)
Grade I	5.3%	14.8%
Grade II	2.6%	11.1%
Grade III A	18.4%	3.7%
Grade III B	10.5%*	7.4% <sup>©</sup>
Grade IV	0	3.7%
Grade V	0	0

P=0.36

No postoperative  
30 day mortality

\*1 patient had intraoperative liver injury died 52 days post op

© 1 patient on adjuvant chemotherapy died of neutropenic sepsis 94 days post surgery

# Key Takeaway Points/Conclusions

**In patients having Locally advanced cT3/4 cN+ Gall Bladder Cancers.**  
Preoperative Chemoradiation and chemotherapy vs. Preoperative Chemotherapy

- Better downstaging
- Better R0 resection rates
- Better Overall and Event Free survival

Preoperative chemoradiation should be preferred over preoperative chemotherapy for improving survival in locally advanced non-metastatic adenocarcinoma of Gall bladder cancers.

# UNRESECTABLE /METASTATIC GBC

Dismal outcomes

Aim of treatment: palliation of symptoms and improvement of QOL

May require drainage to alleviate jaundice

The current standard for unresectable advanced GBC is

palliative intent chemotherapy – *Gemcitabine/Cisplatin or Gem/Oxaliplatin*



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## CLINICAL INVESTIGATION

# A Randomized Study of Consolidation Chemoradiotherapy Versus Observation After First-line Chemotherapy in Advanced Gallbladder Cancers: RACE-GB study



Sushma Agrawal, MD, DNB,<sup>a</sup> Vishwas Kapoor, PhD,<sup>b</sup> Rahul Rahul, MS, MCh,<sup>c</sup> Ashish Singh, MS, MCh,<sup>c</sup> Prabhakar Mishra, PhD,<sup>b</sup> and Rajan Saxena, MS<sup>c</sup>

<sup>a</sup>Departments of Radiotherapy, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India;

<sup>b</sup>Departments of Biostatistics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India; and

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# CONSORT

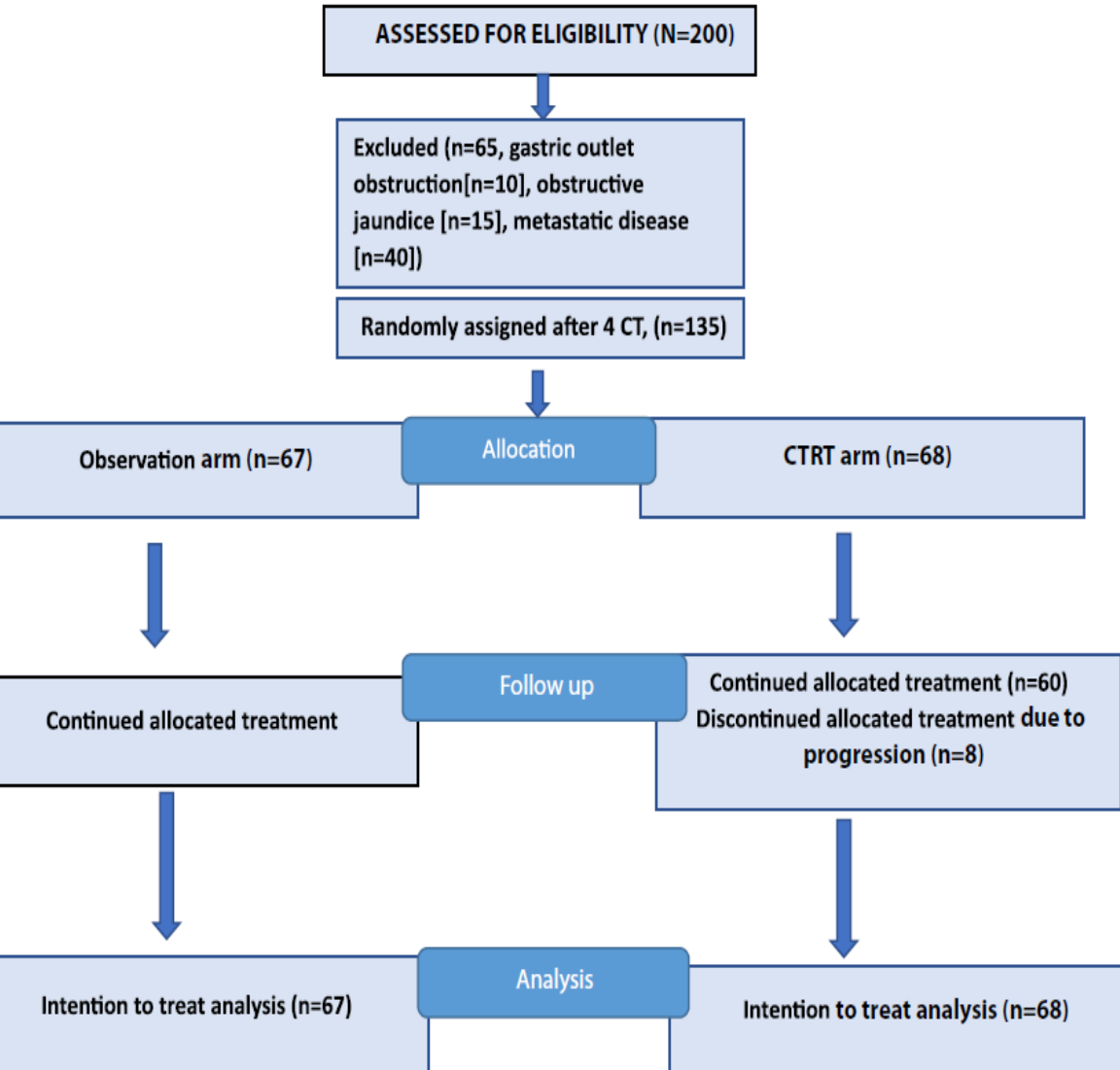
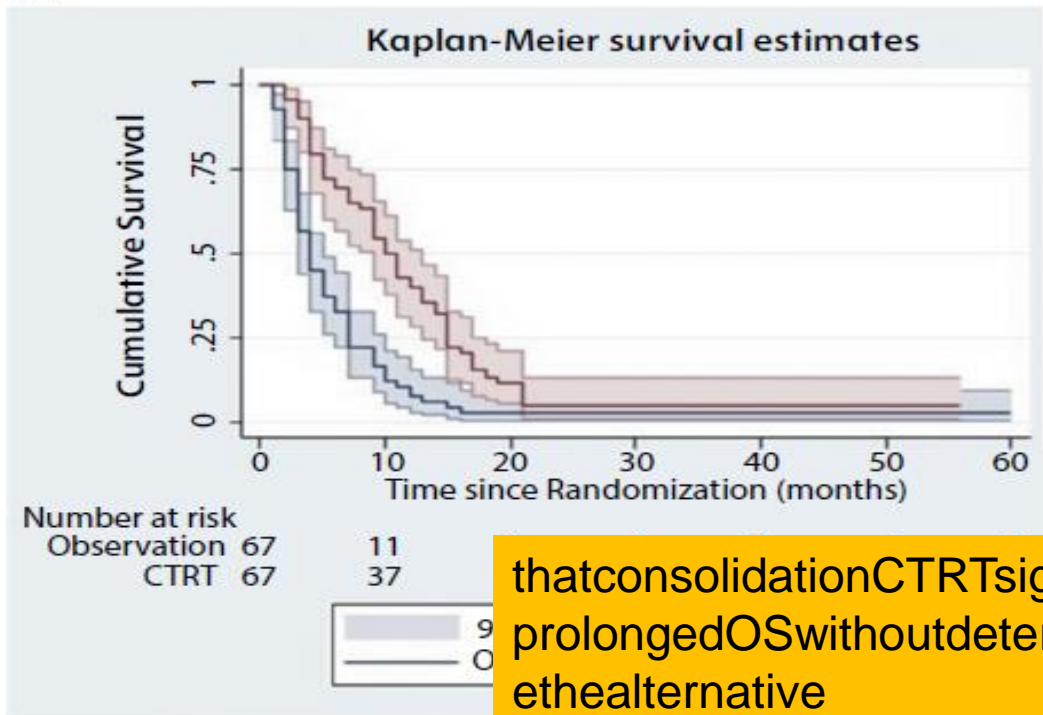


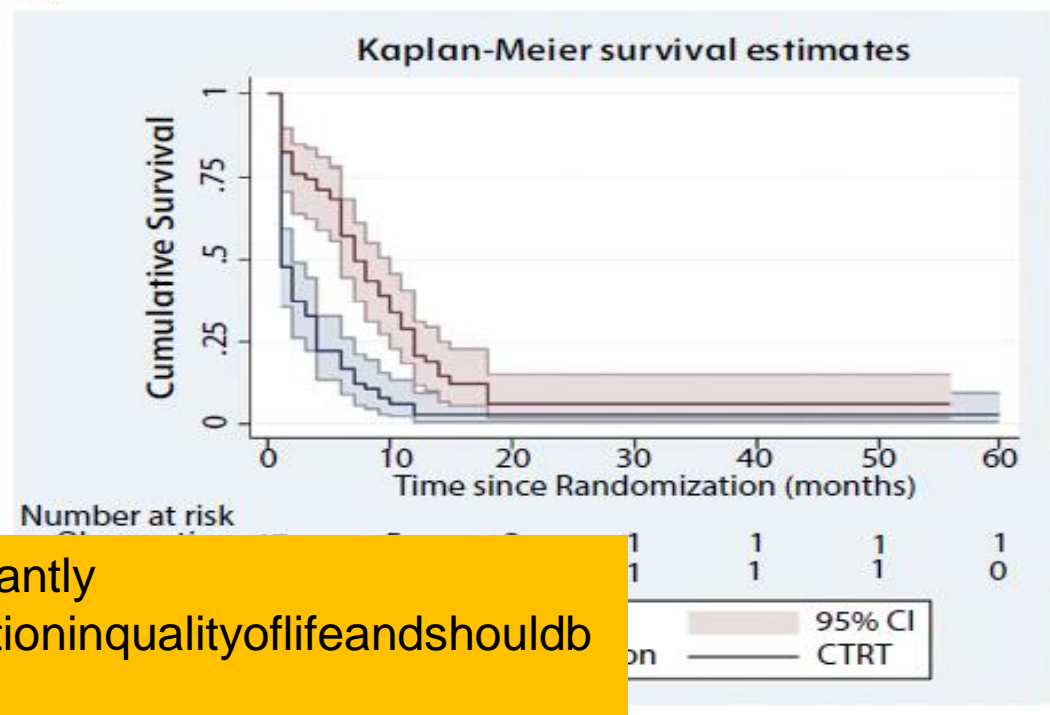
Table 1 Demographic features of both arms

CHARACTERISTICS	Observation (n=67) (%)	CTRT (n=68) (%)	p-value
Age (median, IQR )	54 (IQR 46-64yrs)	52 (IQR 45-62yrs)	
Male	27 (40)	24 (35)	
Female	41 (60)	43 (63)	0.6
Mean Charlson Co-morbidity index	1.63	1.5	0.6
Stenting	16 (24)	21 (31)	0.3
T2	3 (5)	4 (6)	
T3	27 (48)	26 (38)	
T4	37 (55)	38 (56)	0.6
N0	15 (22)	14 (20)	
N1	17 (26)	15 (22)	
N2	28 (42)	25 (38)	
Para-aortic Lymphadenopathy	7 (10)	14 (20)	0.6
M Stage			
Liver (oligo-metastases)	0	7 (10)	0.04

(A)

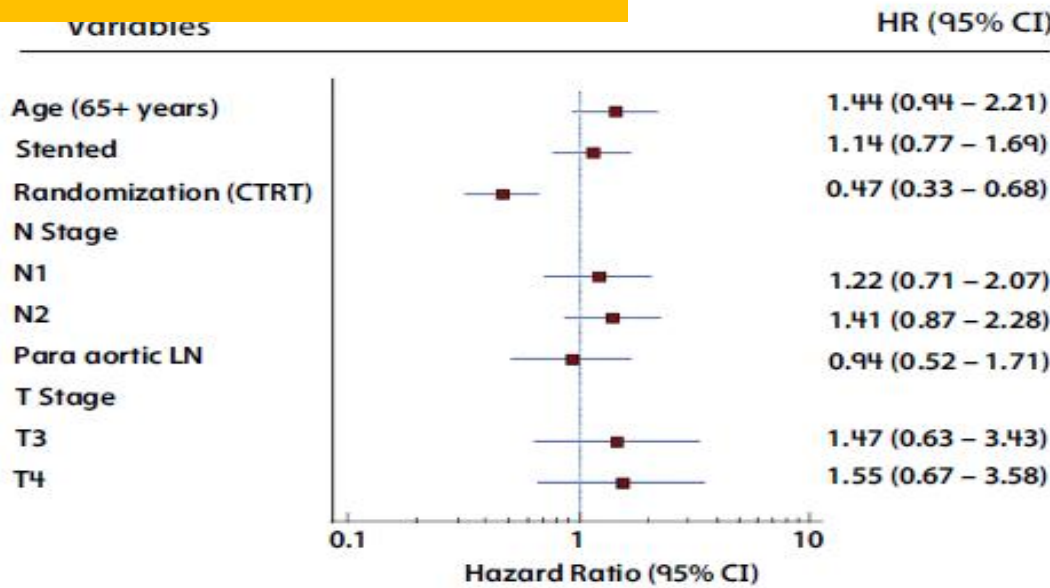
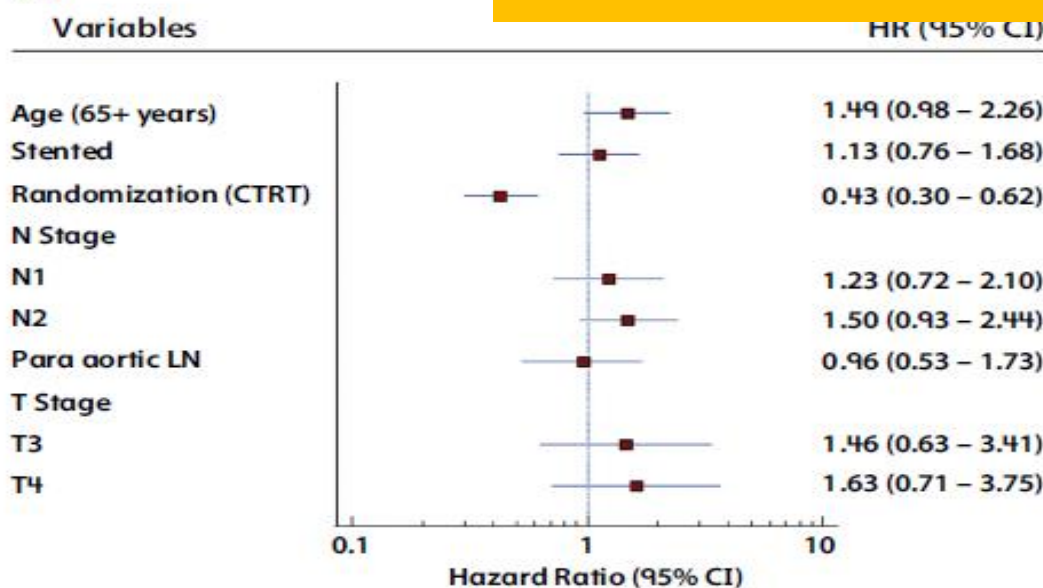


(A)



that consolidation CRTT significantly prolonged OS without deterioration in quality of life and should be the alternative standard of care in advanced unresectable GBC

(B)



# SUMMARY.....



- GBC - Incidence rising- many risk factors are modifiable
- Surveillance for high risk
- Inherent aggressive tumor biology – **Surgical resection current standard of care**
- Adjuvant chemotherapy or Chemoradiation for all resected T1b+ tumors
- Role of NACTRT in down-staging – New standard of care
- For completely unresectable surgery not contemplated- Palliative chemotherapy followed by consolidation chemoradiation should be given