

# Current Evidence on Adjuvant Treatment for Gallbladder Cancer

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# Current status of GB cancer in Korea

- Most common type of bile duct cancer
- Mostly adenocarcinomas
- Incidence of bile duct cancer
  - 6.7/100,000
  - 9<sup>th</sup> most common cancer in Korea
- Incidence of gallbladder cancer
  - 2.96/100,000
  - 40% of entire bile duct cancer

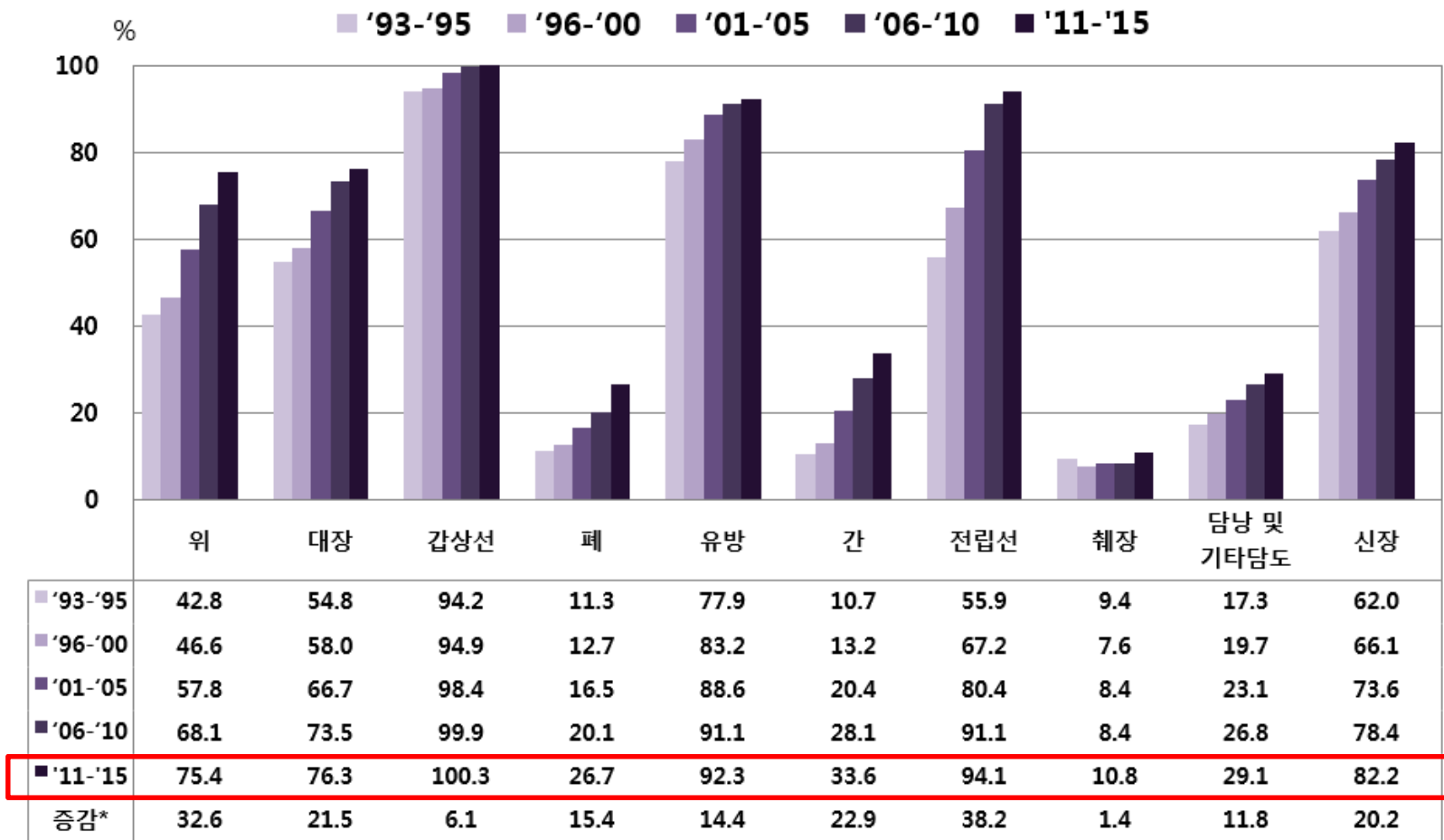
### Incidence

	2005-2008	2009-2013
Localized	21.8%	21.3%
Regional	37.2%	37.7%
Distant	41.0%	41.0%

### 5-year survival rate

	2005-2008	2009-2013
Localized	66.3%	73.5%
Regional	25.0%	35.0%
Distant	3.2%	2.5%

**Overall 5 yr survival rate 28.7%**



\* 증감: '93-'95년 대비 '11-'15년 암발생자의 생존율 차이

**5 yr survival rate similar to lung cancer and only higher than pancreatic cancer**

# Reasons for poor survival

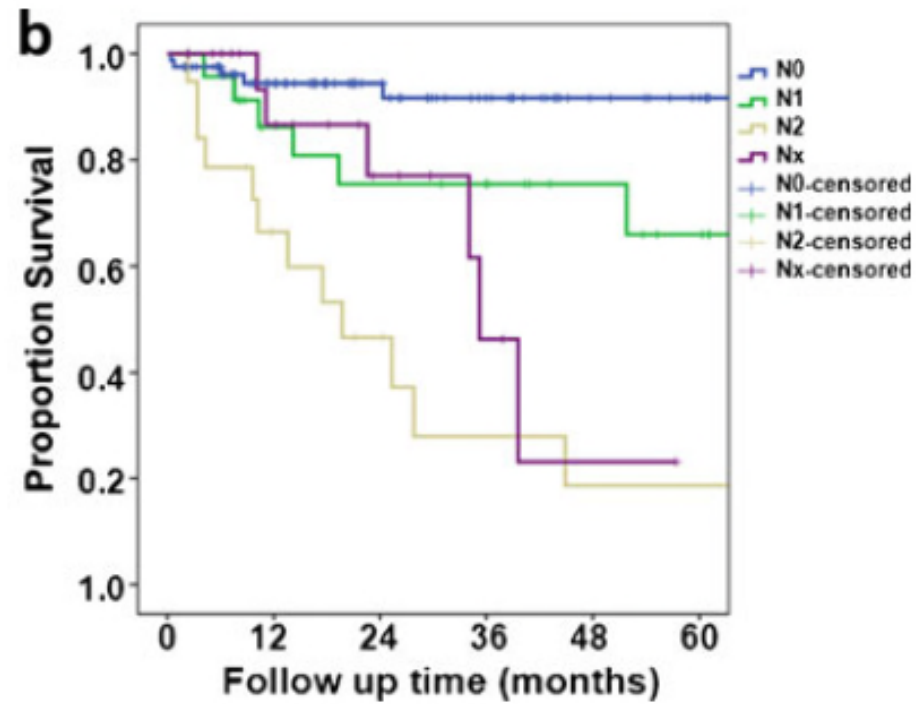
- Low early diagnosis rate
- Not so effective chemotherapy
  - Gemcitabine + cisplatin, the only regimen with proven efficacy
  - No 2<sup>nd</sup> line chemotherapy
- Surgical technique (simple vs radical)
- Early metastasis

# Lymph node metastasis in GB cancer

**Table 3** Cross-table between T and N stages in the seventh edition of TNM staging system

	N stage (%)				Total
	Nx <sup>a</sup>	N0	N1	N2	
T stage (%)					
↑ T1a	6 (33.3)	12 (66.7)	0 (0)	0 (0)	18
T1b	2 (8.3)	18 (75.0)	2 (8.3)	2 (8.3)	24
T2	8 (12.5)	36 (56.3)	13 (20.3)	7 (10.9)	64
↓ T3	4 (15.4)	9 (34.6)	7 (26.9)	6 (23.1)	26
T4	1 (10.0)	4 (40.0)	1 (10.0)	4 (40.0)	10
Total	26 (14.9)	84 (48.3)	28 (16.1)	36 (20.7)	142

LN metastasis of gallbladder cancer starts even when it is confined to muscular layer.



Lymph node metastasis  $\propto$  1 / survival

# To improve survival

- Early diagnosis
  - More localized cancer
- Improved surgical technique
  - Increase complete resection rate and reduce recur rate
- Adjuvant therapy
  - reduce recur rate and prolong survival?

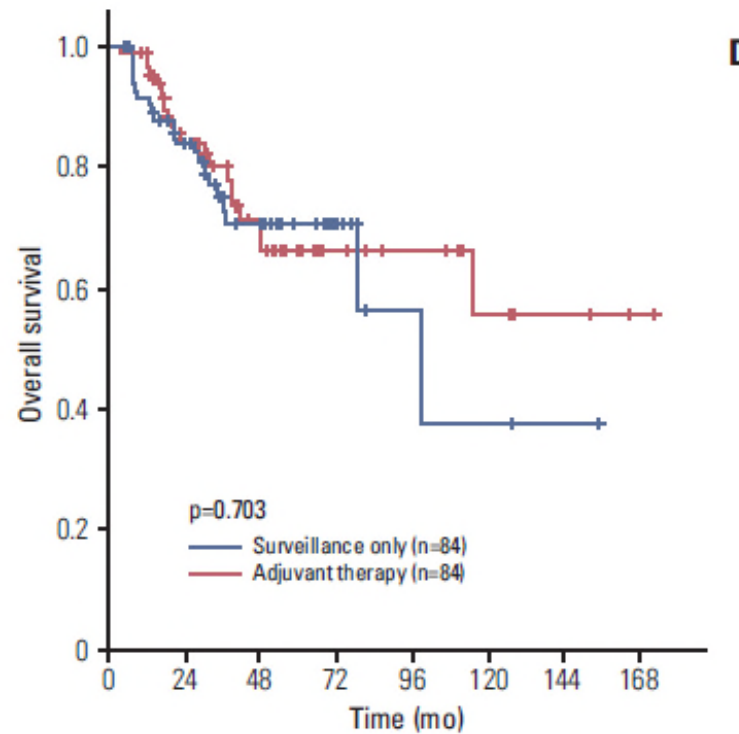


# Does adjuvant therapy works?

- There is no prospective randomized clinical trials to prove its efficacy.
- Most of clinical trials included GB and other biliary cancer altogether.
- Only retrospective study, meta analysis and big data analysis are available.

# Retrospective study

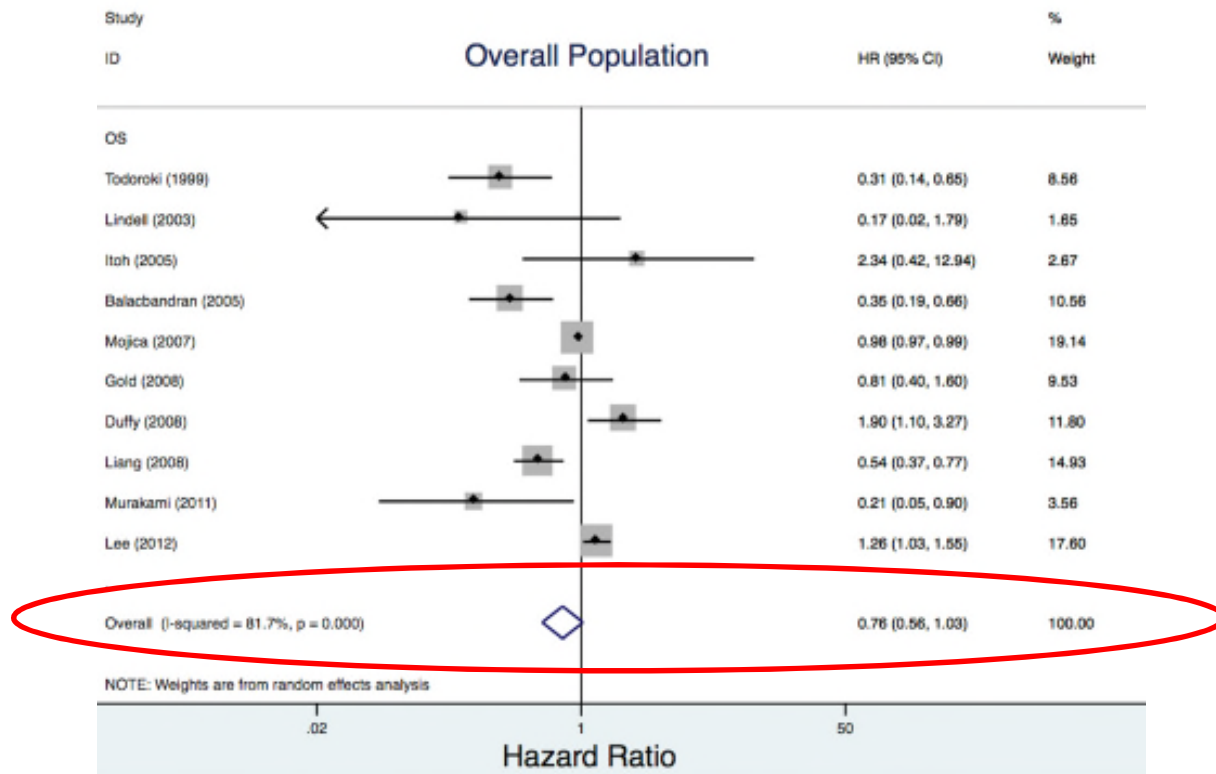
- Multicenter study, Korea
- 441 patients
- Stage I, II, III, R0 disease
- 84 patients with adjuvant therapy vs  
279 patients with no adjuvant therapy

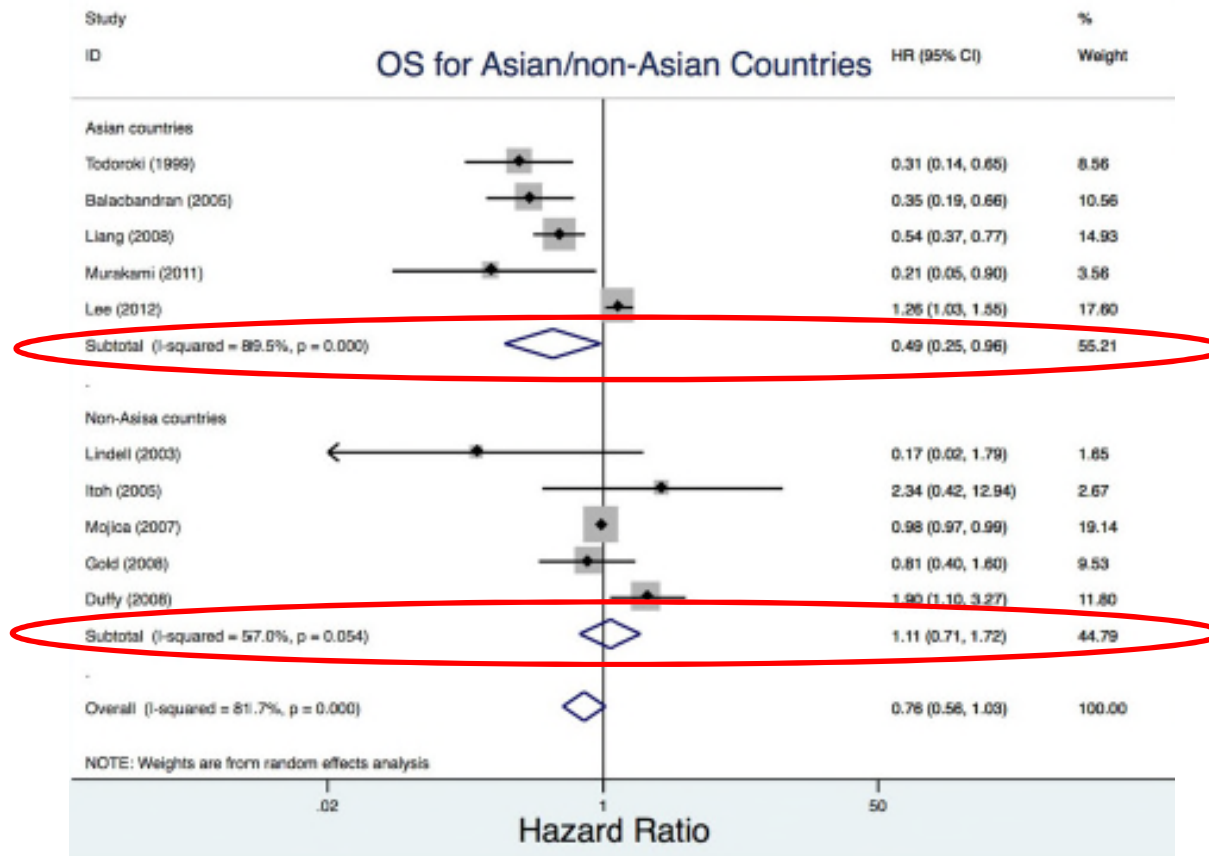


- 5 year survival rate 66.2% vs 70.4% after propensity score matched analysis ( $p = 0.703$ )
- Fluoropyrimidine adjuvant therapy
- Stage III including both LN(+) and (-)

# Meta-analysis

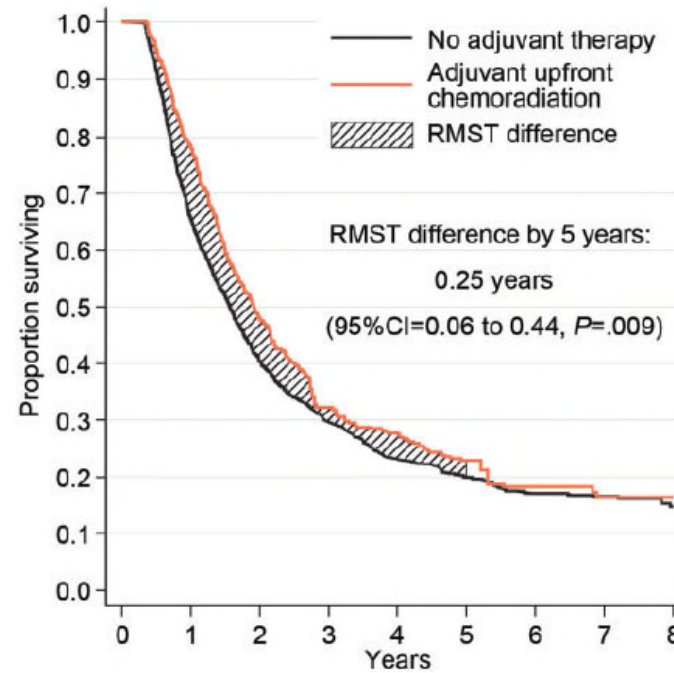
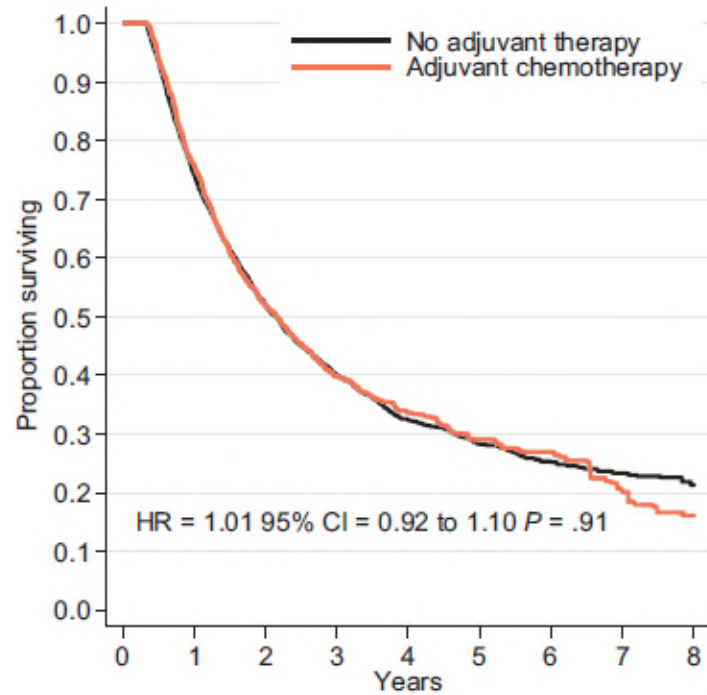
- Ten retrospective studies
- 3,191 patients
- Improvement of OS in Surgery + adjuvant chemotherapy compared to surgery only
- Benefit in node (+), R1 disease, stage  $\geq$  II, Asian countries





# Big data analysis (1)

- American cancer data base
- 20,858 patients
- T1-3 patients (excluding T1N0M0)
- 1373 patients with adjuvant therapy vs 3402 patients with no adjuvant therapy
- No difference in OS
- Maybe benefit of chemoradiotherapy in T3 or LN (+)

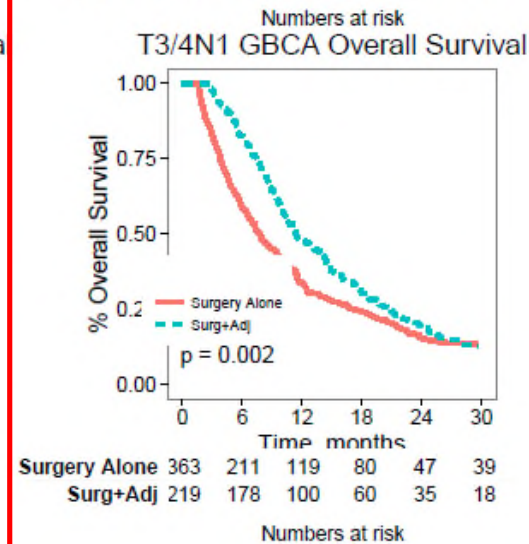
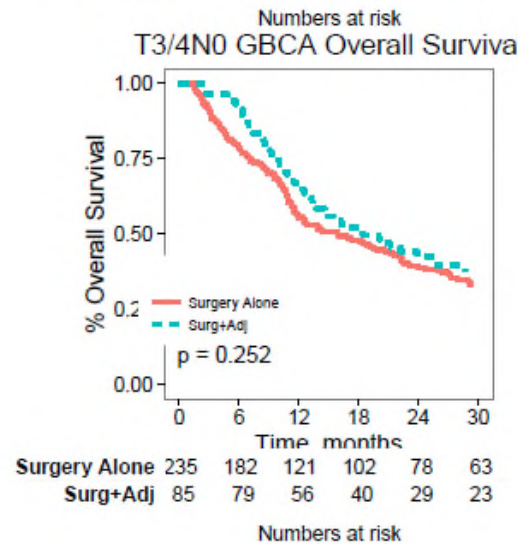
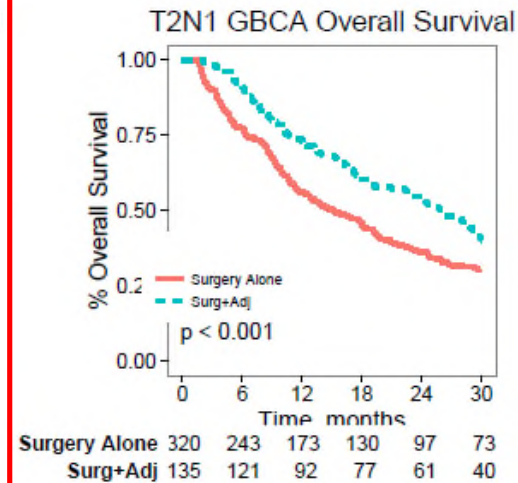
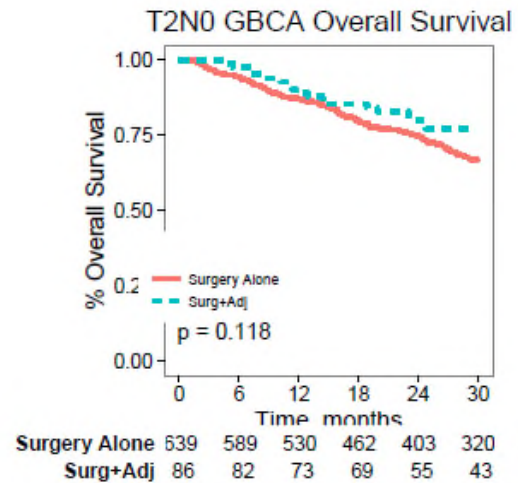


Overall survival not affected by adjuvant therapy.  
Chemoradiotherapy was beneficial in T3 or node positive disease



## Big data analysis (2)

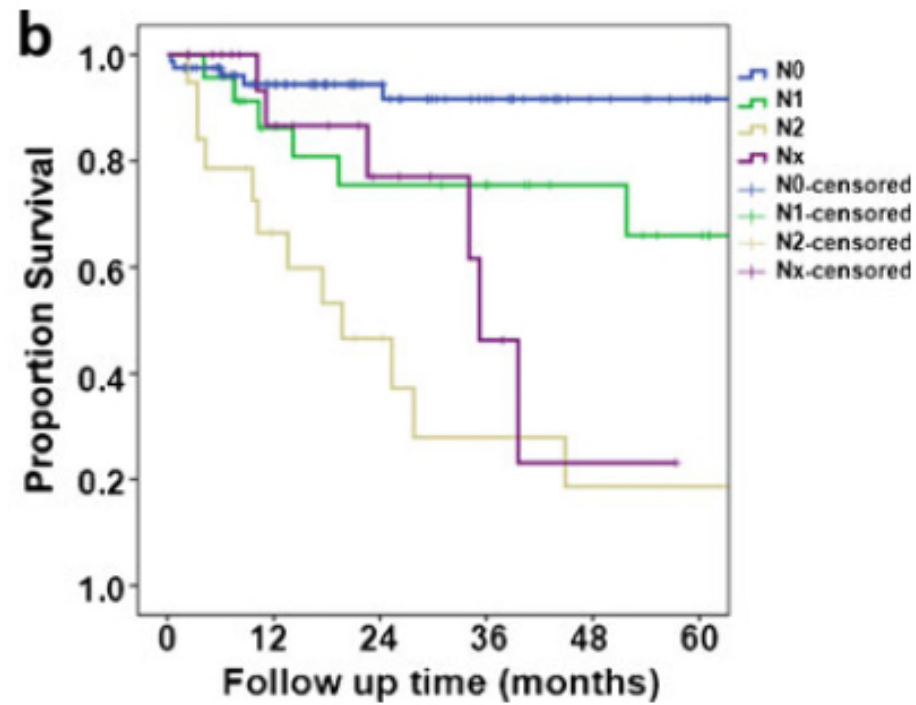
- American cancer data base
- 4,379 patients
- $\geq$  T2 patients
- 967 patients with adjuvant therapy vs 3406 patients with no adjuvant therapy



Variable		N	Hazard Ratio Plot	HR (95% CI)	p
<b>Adjuvant</b>	No Chemo	3406	●	Reference	
	Chemotherapy	967	●	0.86,(0.79, 0.94)	0.001
<b>Age</b>	Under 65	1469	●	Reference	
	65 and Over	2904	●	1.30,(1.20, 1.41)	<0.001
<b>Race</b>	Caucasian	3544	●	Reference	
	African American	538	●	1.08,(0.97, 1.20)	0.15
	Other	291	●	0.88,(0.75, 1.02)	0.10
<b>Gender</b>	Male	1260	●	Reference	
	Female	3113	●	0.94,(0.87, 1.02)	0.13
<b>Charlson_Deyo_Score</b>	0	2933	●	Reference	
	1	1076	●	1.19,(1.09, 1.29)	<0.001
	2+	364	●	1.32,(1.16, 1.49)	<0.001
<b>Node_Status</b>	N0	1045	●	Reference	
	Missing	2291	●	1.83,(1.65, 2.02)	<0.001
	N1+	1037	●	1.93,(1.72, 2.16)	<0.001
<b>Tumor_Grade</b>	Low	2404	●	Reference	
	High	1703	●	1.51,(1.41, 1.63)	<0.001
	Missing	266	●	1.07,(0.92, 1.25)	0.40
<b>Extent</b>	Cholecystectomy	910	●	Reference	
	Radical Cholecystectomy	3463	●	1.03,(0.95, 1.13)	0.47
<b>T_Stage</b>	2	2479	●	Reference	
	3	1706	●	1.89,(1.74, 2.05)	<0.001
	4	188	●	2.71,(2.30, 3.19)	<0.001
<b>Margins</b>	Negative	2732	●	Reference	
	Missing	383	●	1.74,(1.54, 1.96)	<0.001
	Positive	1258	●	1.80,(1.66, 1.96)	<0.001
<b>Facility_Type</b>	Non-Academic Program	2756	●	Reference	
	Academic/Research Program	1572	●	0.83,(0.77, 0.90)	<0.001
	Missing	45	●	0.74,(0.50, 1.09)	0.13

Is Nx = N0 or N1?

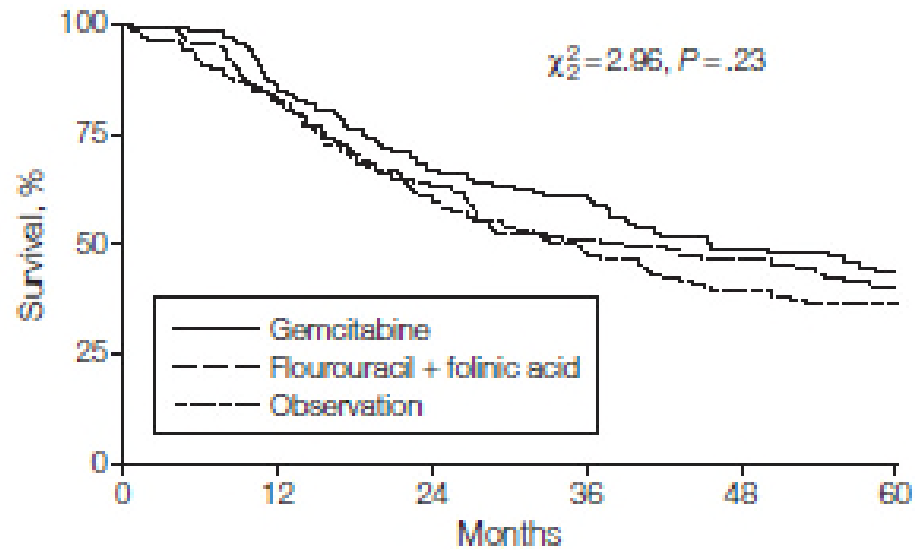
Bergquist et al. Int J Cancer, 2018



- Nx = between N1 and N2, not N0

## ESPAC-3 trial

- Periapillary cancer (22% patients with bile duct cancer)
- Europe
- 5-FU + folinic acid or gemcitabine vs observation
- 143 vs 141 vs 144

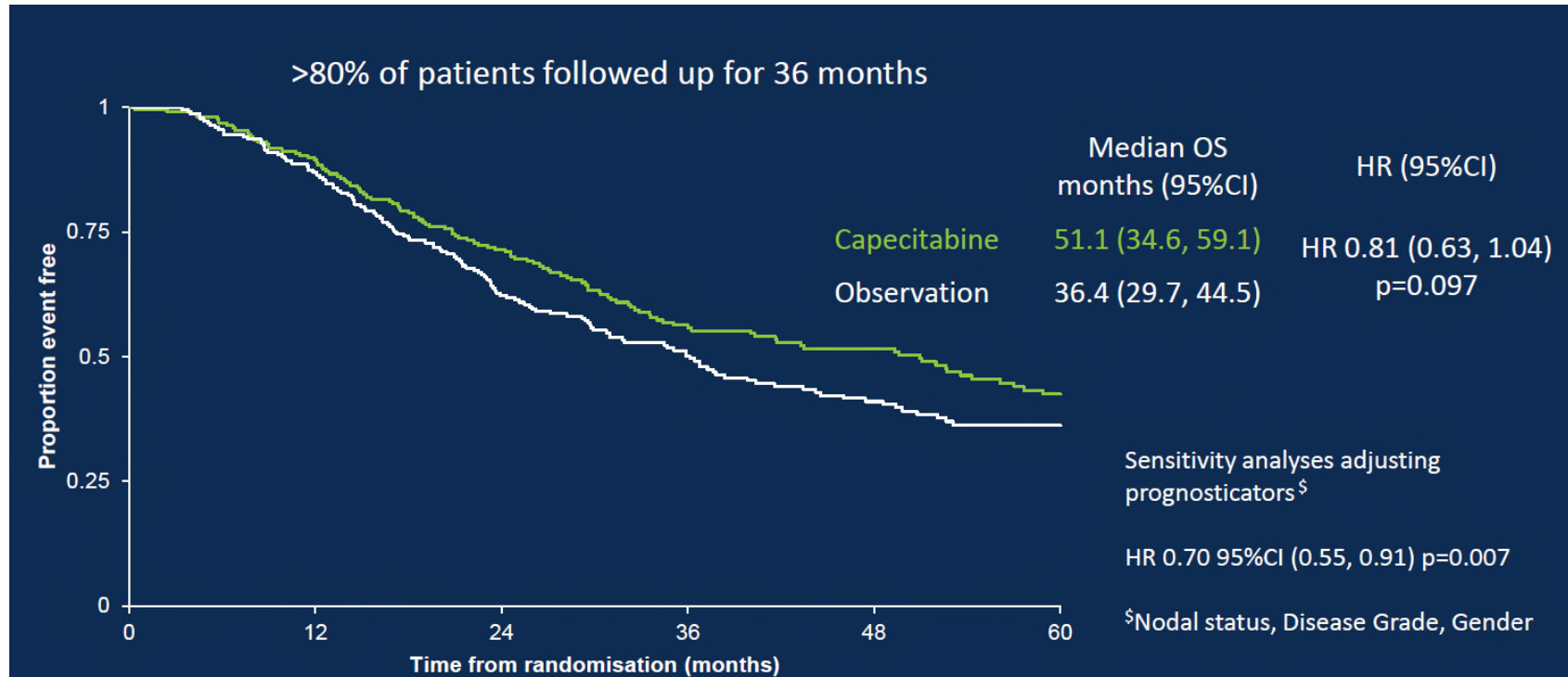


No. at risk						
Gemcitabine	141	119	90	75	50	35
Fluorouracil + folinic acid	143	113	81	65	47	27
Observation	144	116	89	61	48	25

**Survival benefit with gemcitabine adjuvant therapy only in multiple regression analysis.**

# BILCAP trial

- Biliary tract cancer (15% of patients with GB cancer)
- Europe
- Capecitabine vs observation
- Randomization according to tumor site, resection status, PS, and surgery center
- 223 vs 224



Incidence of grade  $\frac{3}{4}$  toxicity was low  
No subgroup analysis was reported



# Conclusion

- Survival of GB cancer is poor.
- Reasons for adjuvant therapy is clear, but evidences that it works are limited.
- Recent trials have shown the hope of survival improvement with adjuvant therapy.
- Finding effective chemotherapeutic agents is a key point.

# Take home messages

- Gemcitabine is a key chemotherapeutic agent for adjuvant therapy
- Capecitabine can be another choice for adjuvant therapy.
- LN involvement is an indication for adjuvant therapy
- Adequate LN sampling is important in deciding whether to do adjuvant therapy.