IASGO, ICUR & KSGC Joint Symposium

Current issues and top-notch management in Gallbladder cancer

Optimal extent of surgery for early gallbladder cancer with regard to long-term survival: A meta-analysis

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Early Gallbladder (GB) Cancer

- The definition of early GB cancer
  - T1 GB cancer?
  - GB cancer confined to the GB?

T stage	
T1 T1a T1b	Tumor invades the lamina propria or muscular layer Tumor invades the lamina propria Tumor invades the muscular layer
T2	Tumor invades perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum) Or the tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

REVIEW
Oncology & Hematology

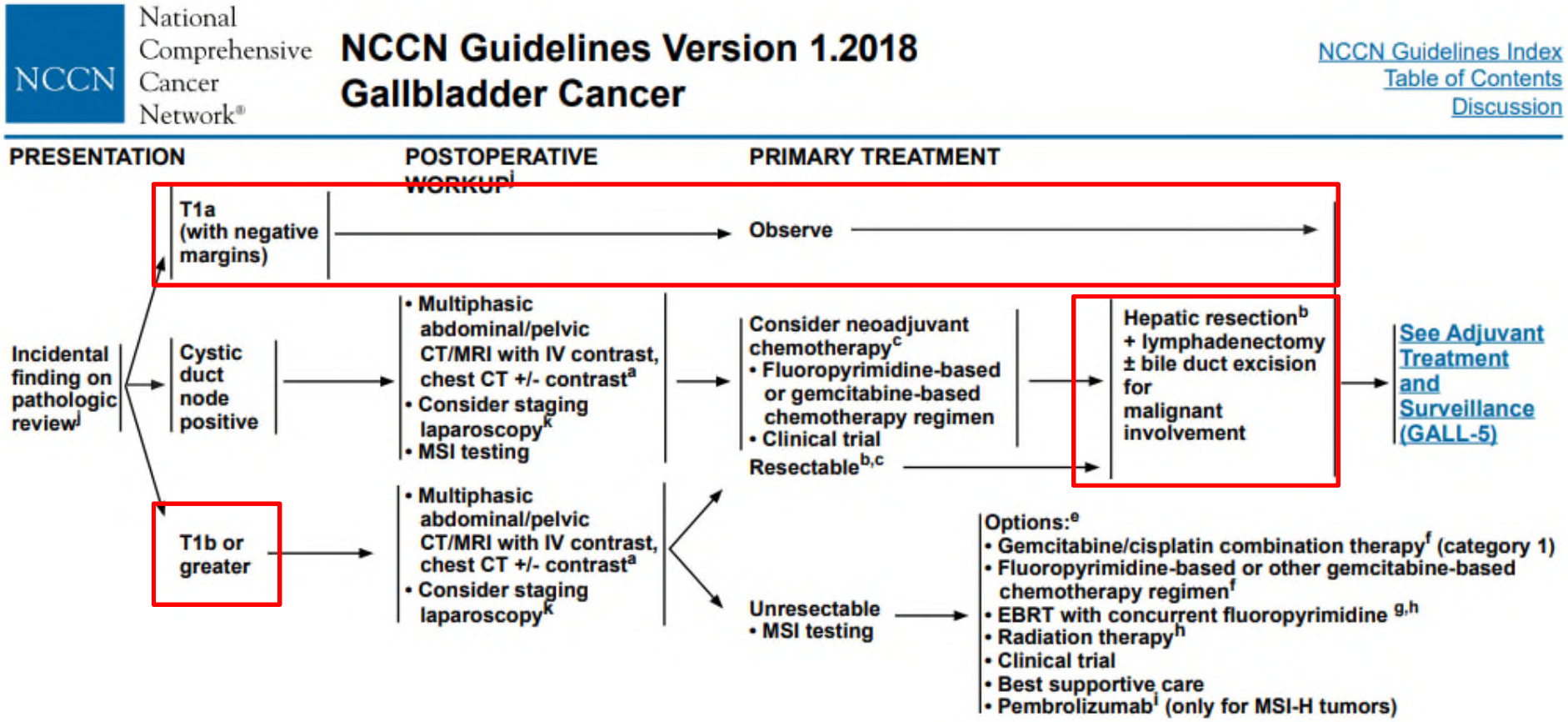
JKMS

http://dx.doi.org/10.3346/jkms.2014.29.10.1333 • J Korean Med Sci 2014; 29: 1333-1340

Practical Guidelines for the Surgical Treatment of Gallbladder Cancer

- Early GB cancer
  - T1a: simple cholecystectomy
  - T1b: controversial
- Advanced GB cancer
  - T2 or above: extended cholecystectomy

NCCN guidelines



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Japanese Society of HBP Surgery

J Hepatobiliary Pancreat Surg (2008) 15:41–54
DOI 10.1007/s00534-007-1279-5

Journal of HBP Surgery

Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment

Satoshi Kondo[1], Tadahiro Takada[2], Masaru Miyazaki[3], Shuichi Miyakawa[4], Kazuhiro Tsukada[5], Masato Nagino[6], Junji Furuse[7], Hiroya Saito[8], Toshio Tsuyuguchi[9], Masakazu Yamamoto[10], Masato Kayahara[11], Fumio Kimura[3], Hideyuki Yoshitomi[3], Satoshi Nozawa[3], Masahiro Yoshida[2], Keita Wada[2], Satoshi Hirano[1], Hodaka Amano[2], and Fumihiko Miura[2]

- T1a GB cancer
  - Simple cholecystectomy
- T1b GB cancer
  - Simple cholecystectomy
- T2 or above
  - Extended cholecystectomy

Germany

S3-Guidelines for Diagnosis and Treatment of Gallstones. German Society for Digestive and Metabolic Diseases and German Society for Surgery of the Alimentary Tract. AWMF Registry 021/008

Authors F. Lammert[1], M. W. Neubrand[2], R. Bittner[3], H. Feussner[4], L. Greiner[5], F. Hagenmüller[6], K. H. Kiehne[7], K. Ludwig[8], H. Neuhaus[9], G. Paumgartner[10], J. F. Riemann[11], T. Sauerbruch[1] für die Teilnehmer der Konsensuskonferenz*

Surg Endosc (2008) 22:2462–2465
DOI 10.1007/s00464-008-9747-9

Immediate re-resection of T1 incidental gallbladder carcinomas: a survival analysis of the German Registry

T. O. Goetze · V. Paolucci

- T1a: simple cholecystectomy
- T1b: radical cholecystectomy

Where lies the controversy?

Country	T1a	T1b	T2 or above
Korea	Simple cholecystectomy	Controversial	Radical cholecystectomy
USA	Simple cholecystectomy	Radical cholecystectomy	Radical cholecystectomy
Japan	Simple cholecystectomy	Simple cholecystectomy	Radical cholecystectomy
Germany	Simple cholecystectomy	Radical cholecystectomy	Radical cholecystectomy

Why am I here?

J Hepatobiliary Pancreat Sci (2018) 25:131–141
DOI: 10.1002/jhbp.521

ORIGINAL ARTICLE

Optimal extent of surgery for early gallbladder cancer with regard to long-term survival: a meta-analysis

Hongeun Lee · Wooil Kwon · Youngmin Han ·
Jae Ri Kim · Sun-Whe Kim · Jin-Young Jang

To evaluate the optimal surgical extent in patients with T1 GB cancer with regard to oncologic safety

T1b GB cancer

For simple cholecystectomy

- Wakai T et al. Br J Surg, 2001
- Ouchi K et al. J Heaptobiliary Pancreat Surg, 2002
- Lee SE et al. Korean J Heatobiliary Pancreat Surg, 2009
- Lee SE et al. World J Gastroenterol, 2011
- Ito H et al. Ann Surg, 2011
- Lee SE et al. Ann Surg Oncol, 2014

For radical cholecystectomy

- Tsunoda T et al. Jpn J Surg, 1987
- Varshney S et al. Eur J Surg Oncol, 2002
- Otero JC et al. J Hepatobiliary Pancreat Surg, 2006
- Hardiman KM et al. J Gastrointest Surg, 2009
- Isambert M et al. J Visc Surg, 2011

Difficulties of investigation

- **Limitations of previous studies**
  - Retrospective in nature
  - Small number of patients
  - Low-level evidence

Table 1 Characteristics of included studies

First author	Affiliation	Study period (publication year)	Total number (*n*)	Mean age (years)	M:F (*n*)	T stage	SC/EC (N/n)	LC/OC (N/n)	5YSR (%)	Death (*n*)
Cangemi et al. [14]	University La Sapienza, Italy	1980–2001 (2006)	15	65.8	5:10	T1a, T1b	T1a: 4/0 T1b: 8/3	N/A	T1a: 100 T1b SC: 37.5 T1b EC: 100	T1a: 0 T1b: 5 (SC: 5, EC: 0)
Cavallaro et al. [15]	University of Catania Medical School, Italy	1998–2008 (2012)	6	T1a: 55 T1b: 65.3	3:3	T1a, T1b	T1a: 2/0	T1a: 2/0 T1b: 1/3	T1a: 100 T1b: 100	T1a: 0 T1b: 0
Chan et al. [16]	Chang Gung Memorial Hospital, Taiwan	1987–2004 (2006)	33	N/A	N/A	T1a, T1b	T1b: 1/3	T1a: 9/5 T1b: 5/14	87.1	T1a: 1 T1b: 2
Coburn et al. [17]	University of Toronto, Canada	1988–2003 (2008)	642	N/A	N/A	T1	613/29	N/A	N/A	SC: 459 EC: 15
Hari et al. [18]	John Wayne Cancer Institute, USA	1988–2008 (2013)	1,115	N/A	N/A	T1a, T1b	T1a: 236/64 T1b: 427/109	N/A	N/A	SC 668 EC: 166 T1a: 207 (SC: 156, EC: 51) T1b: 397 (SC: 319, EC: 78)
Jang et al. [6]	Seoul National University College of Medicine, South Korea	2000–2014 (2016)	195	63.4	85:112	T1a, T1b	T1a: 94/30 T1b: 28/43	T1a: 77/48 T1b: 17/88	T1a: 98.2 T1b: 96.4	T1a: 0 T1b: 0
Kwon et al. [19]	Kansai Medical University, Japan	1992–2004 (2008)	19	T1a: 65.6 T1b: 45	8:11	T1a, T1b	T1a: 17/0 T1b: 2/0	T1a: 17/0 T1b: 2/0	T1a: 100 T1b: 100	T1a: 0 T1b: 0
Otero et al. [20]	Universidad Nacional de Rosario, Argentia	1982–2000 (2006)	51	T1a: 74.2 T1b: 71.8	46:5	T1a, T1b	T1a: 25/0 T1b: 26/0	T1a: 10/15 T1b: 9/17	N/A	T1a: 0 T1b: 9
Ouchi et al. [21]	Tohoku University School of Medicine, Japan	1979–1991 (1994)	8	N/A	N/A	T1	5/3	N/A	SC: 71 EC: 100	SC: 1 EC: 0
Ouchi et al. [22]	Miyagi Cancer Center Hospital, Japan	N/A (2002)	179	N/A	N/A	T1a	167/12	N/A	99	SC: 1 EC: 0
Puhalla et al. [23]	University of Vienna, Austria	1984–1999 (2002)	9	N/A	N/A	T1a, T1b	T1a: 3/0 T1b: 5/1	0/8	N/A	T1a: 0 T1b: 0
Shirai et al. [24]	Niigata University, Japan	1982–2009 (2012)	39	N/A	N/A	T1	39/1	N/A	100	SC: 1 EC: 0
Sun et al. [25]	Yonsei University College of Medicine, South Korea	1995–2003 (2005)	15	N/A	N/A	T1a, T1b	T1a: 10/0 T1b: 5/0	T1a: 10/0 T1b: 5/0	100	T1a: 0 T1b: 0
Suzuki et al. [26]	Fujimnomiya City General Hospital, Japan	1992–1998 (2000)	25	N/A	N/A	T1a, T1b	T1a: 19/0 T1b: 6/0	25/0	92	T1a: 0 T1b: 0
Tantia et al. [27]	ILS multispecialty clinic, India	2004–2007 (2009)	8	T1a: 54.8 T1b: 53.8	4:4	T1a, T1b	T1a: 3/1 T1b: 1/0	16/0	N/A	T1a: 0 T1b: 1 (SC: 0, EC: 1)
Wakai et al. [28]	Niigata University, Japan	1981–1999 (2001)	25	N/A	N/A	T1b	13/12	12/1	N/A	SC: 0 EC: 2
Xu et al. [29]	Peking Union Medial College Hospital, China	1993–2011 (2013	16	N/A	N/A	T1	16/0	16/0	100	SC: 0 EC: 0
Yagi et al. [30]	Keio University, Japan	1990–2004 (2006	13	66	N/A	T1a, T1b	T1a: 12/0 T1b: 1/0	N/A	100	T1a: 0 T1b: 0
Yi et al. [31]	Xiangya Hospital, China	1992–2009 (2013	14	54.5	5:9	T1a, T1b	T1a: 1/2 T1b: 8/3	T1a: 1/2 T1b: 6/5	57.1	T1a: 0 T1b: 8 (EC: 1, SC: 7, LC: 5, OC: 3)
Yoon et al. [32]	Seoul National University Bundang Hospital, South Korea	2004–2014 (2015	45	69	11:34	T1	13/32	N/A	100	T1a: 0 T1b: 0
Yoon et al. [33]	Ulsan University Hospital, South Korea	1997–2010 (2014	54	59.9	27:27	T1b	36/18	19/17	SC: 88.8 EC: 93.3 LC: 84.2 OC: 94.1	SC: 2 EC: 0
You et al. [5]	Samsung Medical Center, South Korea	1998–2007 (2008	52	60.9	25:27	T1a, T1b	T1a: 23/4 T1b: 11/14	T1a: 13/14 T1b: 1/24	T1a: 96.2 T1b: 96	T1a: 1 (SC: 1, EC: 0) T1b: 0

EC extended cholecystectomy, *F* female, *LC* laparoscopic cholecystectomy, *M* male, *OC* open cholecystectomy, *SC* simple cholecystectomy, *5YSR* 5-year survival rate

SEER

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Difficulties of investigation

- **Limitations of previous studies**
  - Retrospective in nature
  - Small number of patients
  - Low-level evidence

- **Difficult to perform randomized clinical trial**
  - Preoperative staging is not reliable
  - Rarity of T1 GB cancer

Differential Diagnostic and Staging Accuracies of High Resolution Ultrasonography, Endoscopic Ultrasonography, and Multidetector Computed Tomography for Gallbladder Polypoid Lesions and Gallbladder Cancer

Jin-Young Jang, MD, PhD, Sun-Whe Kim, MD, PhD,* Seung Eun Lee, MD,* Dae Wook Hwang, MD,* Eun-Jung Kim, MS,* Jae Young Lee, MD, PhD,† Soo Jin Kim, MD, PhD,† Ji Kon Ryu, MD, PhD,‡ and Yong-Tae Kim, MD, PhD‡*

- Diagnostic accuracy of GB cancer depth
  - HRUS: 62.9%
  - EUS: 55.5%
  - CT: 44.4%

- Prediction of T1 GB cancer
  - HRUS: 69.2%
  - EUS: 53.8%
  - CT: not possible

Medicine

OBSERVATIONAL STUDY

OPEN

Impact of Type of Surgery on Survival Outcome in Patients With Early Gallbladder Cancer in the Era of Minimally Invasive Surgery

Oncologic Safety of Laparoscopic Surgery

Jin-Young Jang, MD, PhD, Jin Seok Heo, MD, PhD, Youngmin Han, BS, Jihoon Chang, MD, MS, Jae Ri Kim, MD, Hongbeom Kim, MD, MS, Wooil Kwon, MD, PhD, Sun-Whe Kim, MD, PhD, Seong Ho Choi, MD, PhD, Dong Wook Choi, MD, PhD, Kyoungbun Lee, MD, PhD, Kee-Taek Jang, MD, PhD, Sung-Sik Han, MD, PhD, and Sang-Jae Park, MD, PhD

To collect 197 pathologically proven T1 GB cancer

- 3 major tertiary referral hospitals
- 2000 to 2014

Difficulties of investigation

- **Limitations of previous studies**
  - Retrospective in nature
  - Small number of patients
  - Low-level evidence
- **Difficult to perform randomized clinical trial**
  - Preoperative staging is not reliable
  - Rarity of T1 GB cancer
- **Inaccurate and unreliable results**
  - Pathologic diagnosis is extremely challenging

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Optimal extent of surgery for early gallbladder cancer with regard to long-term survival: a meta-analysis

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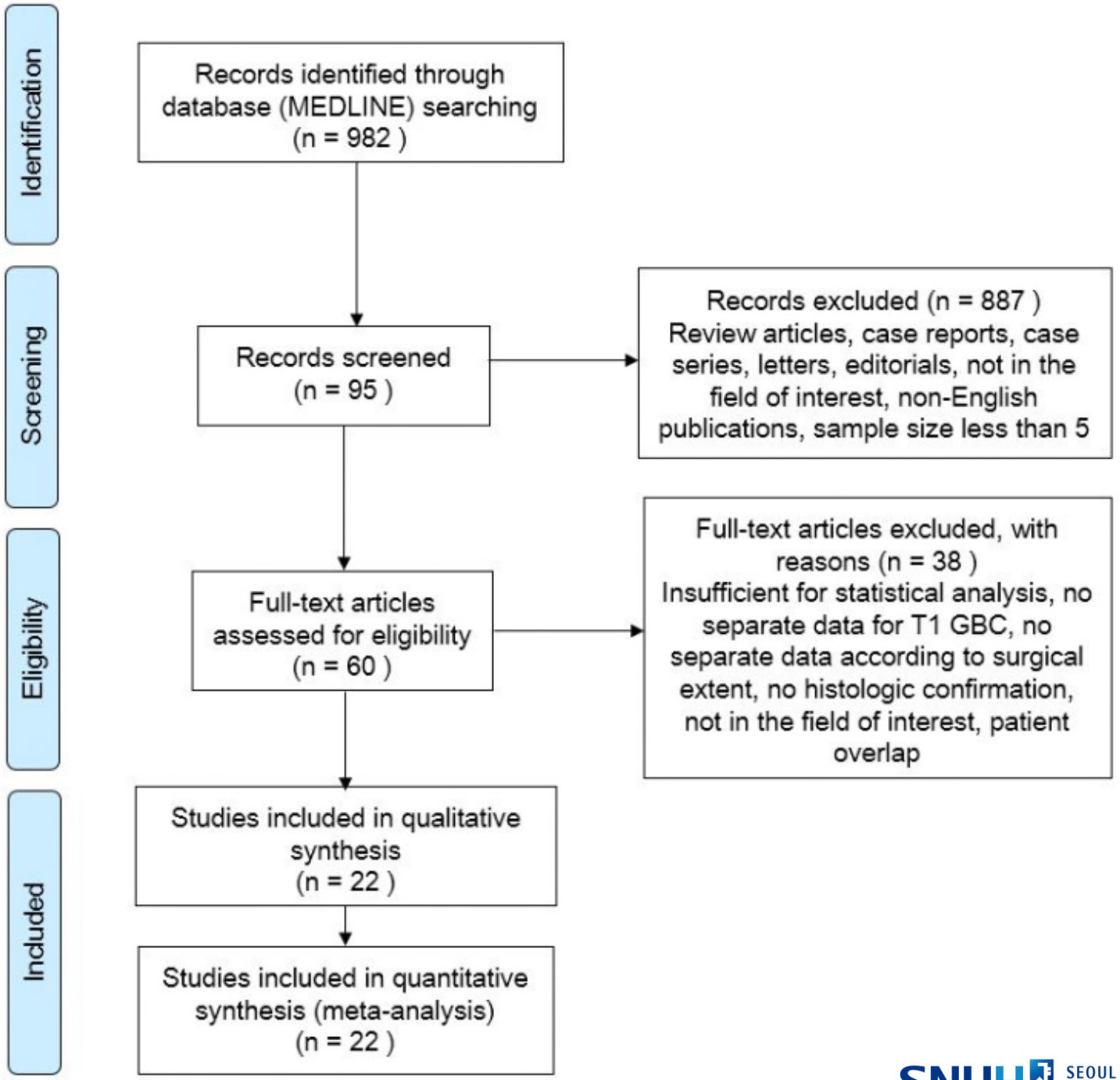
Jae Ri Kim · Sun-Whe Kim · Jin-Young Jang

We performed a meta-analysis to evaluate the optimal surgical extent in patients with T1 GB cancer with regard to oncologic safety

Literature search strategy

- PUBMED
- Search keyword
  - (Early gallbladder cancer OR T1 gallbladder cancer) AND (survival) AND (cholecystectomy)
  - (Early gallbladder cancer) AND (cholecystectomy OR surgery)
  - (T1 gallbladder cancer) AND (cholecystectomy OR surgery)
  - (Early gallbladder cancer) AND (laparoscop*)
  - (T1 gallbladder cancer) AND (laparoscop*)
  - (Gallbladder carcinoma) AND (cholecystectomy OR surgery) AND (T1)
  - (Gallbladder carcinoma) AND (T1)
- Publication date: 1990-present



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Included studies

- 22 studies with 2,578 patients with T1a or T1b GB cancer
  - 5 studies from Western countries
    - The USA, Canada, Italy, Argentina, Austria
  - 17 studies from Eastern countries
    - Korea, Japan, China, Taiwan, India
- 18 studies with descriptive analysis on 2,270 T1 GBC patients
  - 14 publications on T1a
  - 15 publications on T1b
- Patient demographics
  - Mean age: 55.0-74.2 years
  - Male-to-female ratio: 1:1.1

Table 1 Characteristics of included studies

First author	Affiliation	Study period (publication year)	Total number (*n*)	Mean age (years)	M:F (*n*)	T stage	SC/EC (N/n)	LC/OC (N/n)	5YSR (%)	Death (*n*)
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Wakai et al. [28]	Niigata University, Japan	1981–1999 (2001)	25	N/A	N/A	T1b	13/12	12/1	N/A	SC: 0 EC: 2
Xu et al. [29]	Peking Union Medial College Hospital, China	1993–2011 (2013)	16	N/A	N/A	T1	16/0	16/0	100	SC: 0 EC: 0
Yagi et al. [30]	Keio University, Japan	1990–2004 (2006)	13	66	N/A	T1a, T1b	T1a: 12/0 T1b: 1/0	N/A	100	T1a: 0 T1b: 0
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You et al. [5]	Samsung Medical Center, South Korea	1998–2007 (2008)	52	60.9	25:27	T1a, T1b	T1a: 23/4 T1b: 11/14	T1a: 13/14 T1b: 1/24	T1a: 96.2 T1b: 96	T1a: 1 (SC: 1, EC: 0) T1b: 0

EC extended cholecystectomy, *F* female, *LC* laparoscopic cholecystectomy, *M* male, *OC* open cholecystectomy, *SC* simple cholecystectomy, *5YSR* 5-year survival rate

Data extraction and synthesis

- Data extraction
  - Two independent reviewers extracted the data according to predefined inclusion criteria

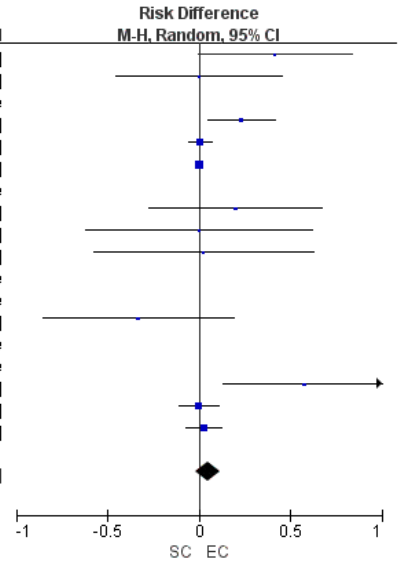
- Data synthesis
  - Risk ratio and risk difference between simple and extended cholecystectomy for T1 GBC
  - Subgroup analysis of T1a and T1b GBC
  - Dichotomous data on cancer-related deaths

T1 GB cancer

(a)

Study or Subgroup	SC Events	SC Total	EC Events	EC Total	Weight	Risk Difference M-H, Random, 95% CI
Cangemi 2006	5	12	0	3	2.4%	0.42 [-0.00, 0.84]
Cavallaro 2012	0	3	0	3	2.1%	0.00 [-0.46, 0.46]
Chan 2006	3	33	0	0		Not estimable
Coburn 2008	459	613	15	29	9.0%	0.23 [0.05, 0.42]
Hari 2013	668	892	166	223	20.8%	0.00 [-0.06, 0.07]
Jang 2016	0	122	0	73	24.8%	0.00 [-0.02, 0.02]
Kwon 2008	0	19	0	0		Not estimable
Ouchi 1994	1	5	0	3	2.0%	0.20 [-0.27, 0.67]
Puhalla 2002	0	8	0	1	1.2%	0.00 [-0.62, 0.62]
Shirai 2012	1	39	0	1	1.2%	0.03 [-0.58, 0.63]
Sun 2005	0	15	0	0		Not estimable
Suzuki 2000	0	25	0	0		Not estimable
Tantia 2009	0	5	1	3	1.6%	-0.33 [-0.86, 0.19]
Xu 2013	0	16	0	0		Not estimable
Yagi 2006	0	13	0	0		Not estimable
Yi 2013	7	9	1	5	2.2%	0.58 [0.13, 1.02]
Yoon 2015	0	13	0	32	15.9%	0.00 [-0.11, 0.11]
You 2008	1	34	0	18	16.7%	0.03 [-0.07, 0.13]
Total (95% CI)		**1876**		**394**	**100.0%**	**0.05 [-0.02, 0.12]**
Total events	1145		183			

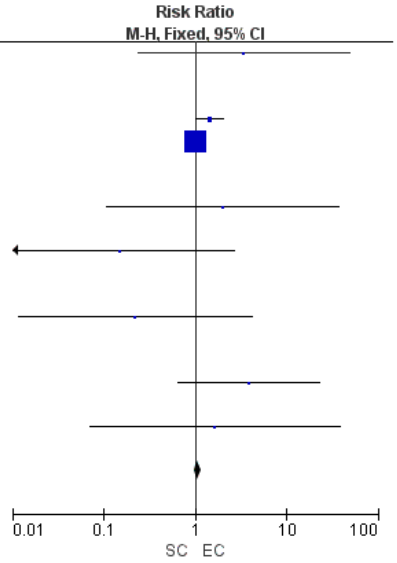
Heterogeneity: Tau² = 0.00; Chi² = 27.27, df = 11 (P = 0.004); I² = 60%
Test for overall effect: Z = 1.37 (P = 0.17)



(b)

Study or Subgroup	SC Events	SC Total	EC Events	EC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cangemi 2006	5	12	0	3	0.3%	3.38 [0.23, 48.84]
Cavallaro 2012	0	3	0	3		Not estimable
Chan 2006	3	33	0	0		Not estimable
Coburn 2008	459	613	15	29	9.5%	1.45 [1.02, 2.06]
Hari 2013	668	892	166	223	88.4%	1.01 [0.92, 1.10]
Jang 2016	0	122	0	73		Not estimable
Kwon 2008	0	19	0	0		Not estimable
Ouchi 1994	1	5	0	3	0.2%	2.00 [0.11, 37.83]
Puhalla 2002	0	8	0	1		Not estimable
Shirai 2012	1	39	0	1	0.3%	0.15 [0.01, 2.64]
Sun 2005	0	15	0	0		Not estimable
Suzuki 2000	0	25	0	0		Not estimable
Tantia 2009	0	5	1	3	0.6%	0.22 [0.01, 4.20]
Xu 2013	0	16	0	0		Not estimable
Yagi 2006	0	13	0	0		Not estimable
Yi 2013	7	9	1	5	0.4%	3.89 [0.65, 23.23]
Yoon 2015	0	13	0	32		Not estimable
You 2008	1	34	0	18	0.2%	1.63 [0.07, 38.06]
Total (95% CI)		**1876**		**394**	**100.0%**	**1.06 [0.97, 1.16]**
Total events	1145		183			

Heterogeneity: Chi² = 10.35, df = 7 (P = 0.17); I² = 32%
Test for overall effect: Z = 1.36 (P = 0.17)



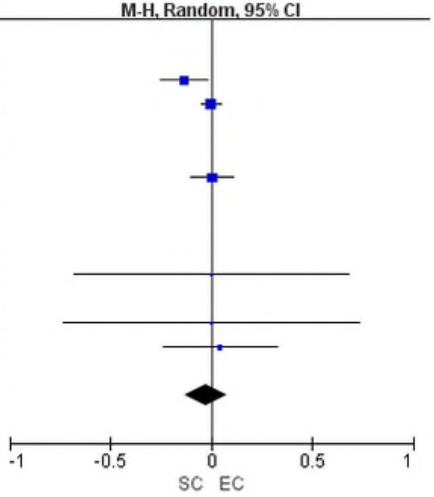
T1a GB cancer

(a)

Study or Subgroup	SC Events	SC Total	EC Events	EC Total	Weight	Risk Difference M-H, Random, 95% CI
Cangemi 2006	0	4	0	0		Not estimable
Cavallaro 2012	0	2	0	0		Not estimable
Hari 2013	156	236	51	64	25.2%	-0.14 [-0.25, -0.02]
Jang 2016	0	94	0	30	33.9%	0.00 [-0.05, 0.05]
Kwon 2008	0	17	0	0		Not estimable
Otero 2006	0	25	0	0		Not estimable
Ouchi 2002	1	167	0	12	26.6%	0.01 [-0.10, 0.11]
Puhalla 2002	0	3	0	0		Not estimable
Sun 2005	0	10	0	0		Not estimable
Suzuki 2000	0	19	0	0		Not estimable
Tantia 2009	0	3	0	1	2.2%	0.00 [-0.68, 0.68]
Yagi 2006	0	12	0	0		Not estimable
Yi 2013	0	1	0	2	1.9%	0.00 [-0.73, 0.73]
You 2008	1	23	0	4	10.1%	0.04 [-0.24, 0.32]
Total (95% CI)		**616**		**113**	**100.0%**	**-0.03 [-0.13, 0.08]**
Total events	158		51			

Heterogeneity: Tau² = 0.01; Chi² = 13.83, df = 5 (P = 0.02); I² = 64%

Test for overall effect: Z = 0.53 (P = 0.60)

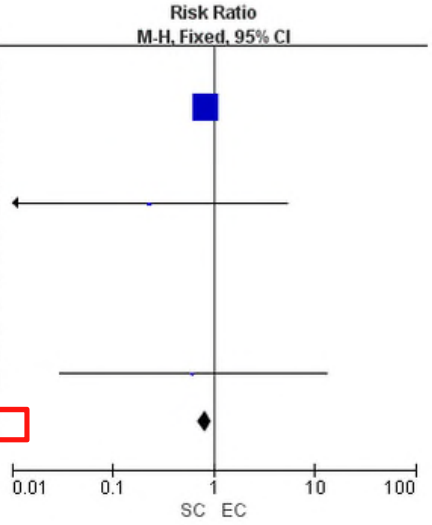


(b)

Study or Subgroup	SC Events	SC Total	EC Events	EC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cangemi 2006	0	4	0	0		Not estimable
Cavallaro 2012	0	2	0	0		Not estimable
Hari 2013	156	236	51	64	97.9%	0.83 [0.71, 0.97]
Jang 2016	0	94	0	30		Not estimable
Kwon 2008	0	17	0	0		Not estimable
Otero 2006	0	25	0	0		Not estimable
Ouchi 2002	1	167	0	12	1.1%	0.23 [0.01, 5.42]
Puhalla 2002	0	3	0	0		Not estimable
Sun 2005	0	10	0	0		Not estimable
Suzuki 2000	0	19	0	0		Not estimable
Tantia 2009	0	3	0	1		Not estimable
Yagi 2006	0	12	0	0		Not estimable
Yi 2013	0	1	0	2		Not estimable
You 2008	1	23	0	4	1.0%	0.63 [0.03, 13.23]
Total (95% CI)		**616**		**113**	**100.0%**	**0.82 [0.70, 0.96]**
Total events	158		51			

Heterogeneity: Chi² = 0.67, df = 2 (P = 0.72); I² = 0%

Test for overall effect: Z = 2.50 (P = 0.01)

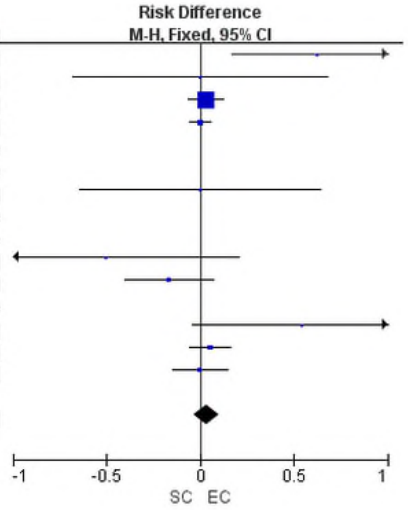


T1b GB cancer

(a)

Study or Subgroup	SC Events	SC Total	EC Events	EC Total	Weight	Risk Difference M-H, Fixed, 95% CI
Cangemi 2006	5	8	0	3	1.6%	0.63 [0.17, 1.08]
Cavallaro 2012	0	1	0	3	0.6%	0.00 [-0.68, 0.68]
Hari 2013	319	427	78	109	64.3%	0.03 [-0.06, 0.13]
Jang 2016	0	28	0	43	12.5%	0.00 [-0.06, 0.06]
Kwon 2008	0	2	0	0		Not estimable
Otero 2006	9	26	0	0		Not estimable
Puhalla 2002	0	5	0	1	0.6%	0.00 [-0.64, 0.64]
Sun 2005	0	5	0	0		Not estimable
Suzuki 2000	0	6	0	0		Not estimable
Tantia 2009	0	2	1	2	0.7%	-0.50 [-1.21, 0.21]
Wakai 2001	0	13	2	12	4.6%	-0.17 [-0.40, 0.07]
Yagi 2006	0	1	0	0		Not estimable
Yi 2013	7	8	1	3	1.6%	0.54 [-0.04, 1.12]
Yoon 2014	2	36	0	18	8.9%	0.06 [-0.05, 0.16]
You 2008	0	11	0	14	4.6%	0.00 [-0.15, 0.15]
Total (95% CI)		**579**		**208**	**100.0%**	**0.03 [-0.03, 0.10]**
Total events	342		82			

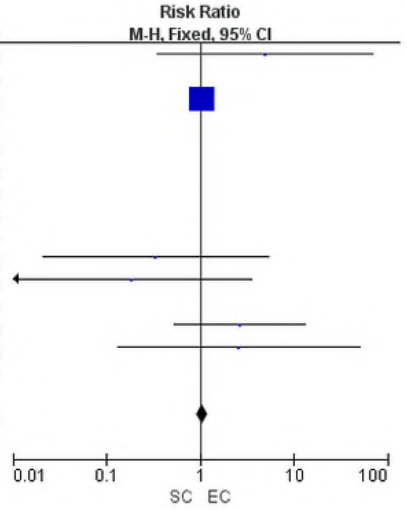
Heterogeneity: Chi² = 16.08, df = 9 (P = 0.07); I² = 44%
Test for overall effect: Z = 0.97 (P = 0.33)



(b)

Study or Subgroup	SC Events	SC Total	EC Events	EC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cangemi 2006	5	8	0	3	0.5%	4.89 [0.35, 68.83]
Cavallaro 2012	0	1	0	3		Not estimable
Hari 2013	319	427	78	109	94.7%	1.04 [0.92, 1.19]
Jang 2016	0	28	0	43		Not estimable
Kwon 2008	0	2	0	0		Not estimable
Otero 2006	9	26	0	0		Not estimable
Puhalla 2002	0	5	0	1		Not estimable
Sun 2005	0	5	0	0		Not estimable
Suzuki 2000	0	6	0	0		Not estimable
Tantia 2009	0	2	1	2	1.1%	0.33 [0.02, 5.33]
Wakai 2001	0	13	2	12	2.0%	0.19 [0.01, 3.52]
Yagi 2006	0	1	0	0		Not estimable
Yi 2013	7	8	1	3	1.1%	2.63 [0.52, 13.29]
Yoon 2014	2	36	0	18	0.5%	2.57 [0.13, 50.83]
You 2008	0	11	0	14		Not estimable
Total (95% CI)		**579**		**208**	**100.0%**	**1.06 [0.93, 1.22]**
Total events	342		82			

Heterogeneity: Chi² = 4.91, df = 5 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)



Conclusion from the result

T	Optimal extent of surgery
T1	Simple cholecystectomy ≒ Radical cholecystectomy
T1a	Simple cholecystectomy ≥ Radical cholecystectomy
T1b	Simple cholecystectomy ≒ Radical cholecystectomy

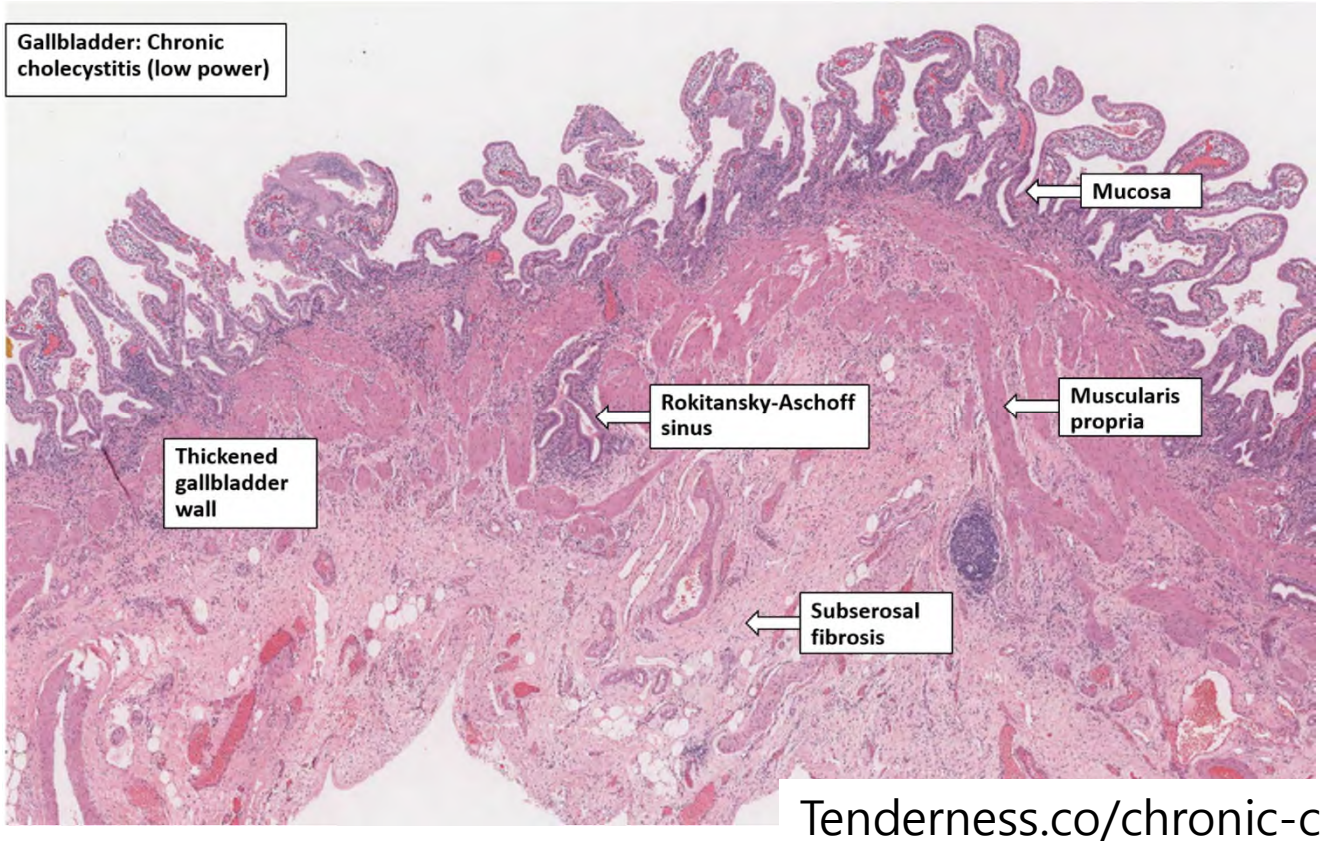
If so, because simple cholecystectomy offers less morbidity to the patient, simple cholecystectomy should be favored over radical cholecystectomy

Can this conclusion be trusted?

- Are simple cholecystectomies really simple?
- Are survival data cancer-related?
- Pooled risk ratio may be misinterpreted due to lack of events
- Are pathologic data really accurate?

Pathologically challenges (I)

- Anatomy
  - Thin wall
  - Rokitansky-Aschoff sinus

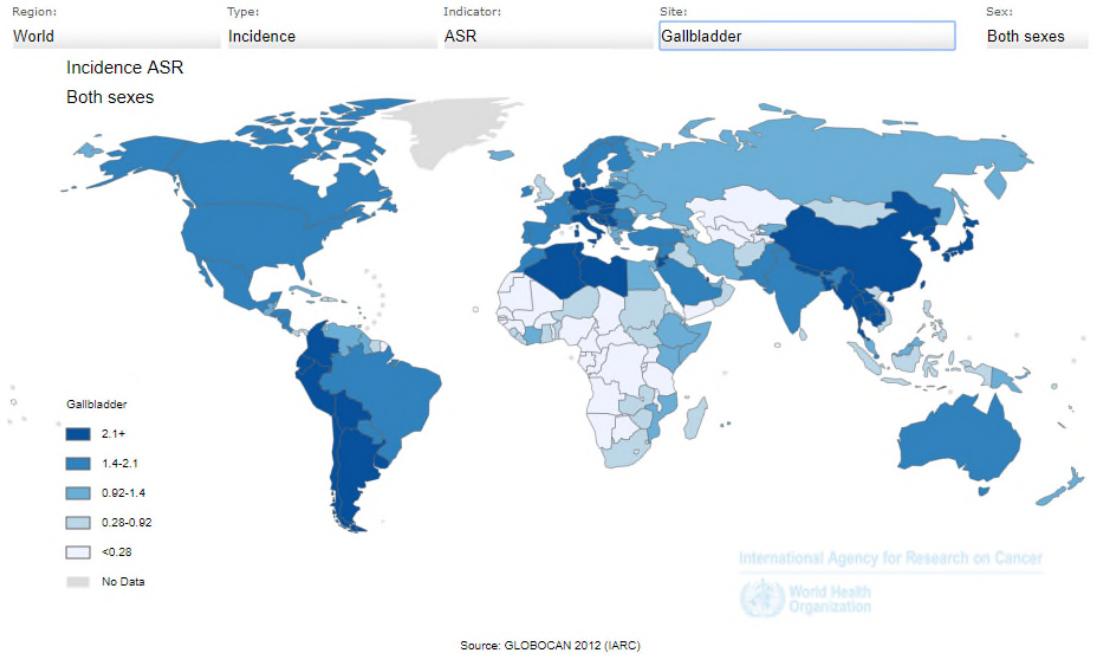


Tenderness.co/chronic-cholecystitis/

Pathologically challenges (II)

- In low incidence area, microscopic evaluations are omitted or over-simplified
- Missed incidental early GB cancer due to inadequate sectioning
- Over 1/3 advanced GB cancers are missed during gross examination, and about 70% of early GB cancers are missed
- Undersampling
  - Under-diagnosis
  - Under-staging

Pathologically challenges (III)



- Low-incidence countries (Europe and North America)
  - Undersampling → Understaging
  - 5-YSR of T1b cancer: 35%

- High-incidence countries (Korea, Japan, India and Chile)
  - Full mapping → less Undersampling → less Understaging
  - 10-YSR: 90%

DOI:10.1111/hpb.12444 HPB

ORIGINAL ARTICLE

Gallbladder Cancer: expert consensus statement

Thomas A. Aloia[1], Nicolas Járufe[2], Milind Javle[3], Shishir K. Maithel[4], Juan C. Roa[5], Volkan Adsay[6], Felipe J. F. Coimbra[7] & William R. Jarnagin[8]

[1]Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2] Department of Digestive Surgery, School of Medicine, Catholic University of Chile (Pontificia Universidad Católica de Chile), Santiago, Chile, [3]Department of GI Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA, [4]Department of Surgery, Winship Cancer Institute, Emory University, Atlanta, GA, USA, [5]Department of Digestive Surgery, School of Medicine, Catholic University of Chile (Pontificia Universidad Catolica de Chile), Santiago, Chile, [6]Department of Pathology and Laboratory Medicine, Winship Cancer Institute, Emory University, Atlanta, GA, USA, [7]Department of Abdominal Surgery, AC Camargo Cancer Centre, São Paulo, Brazil, and [8]Department of Surgery, Memorial Sloan–Kettering Cancer Center, New York, NY, USA

Consensus statements

- Particularly in areas of high incidence, routine gallbladder specimens should be pathologically assessed and the minimum examination should include the microscopic evaluation of three sections and the cystic duct margin.
- During the initial analysis, a finding of high-grade dysplasia, hyalinizing cholecystitis and/or neoplastic polyps should prompt the complete sampling of the entire gallbladder specimen to accurately stage any associated invasive malignancy.
- Gallbladder specimens with proven cancer should be extensively sampled and prognostic factors determined, including microscopic depth of tumour invasion, tumour involvement of the cystic duct margin, involvement of Rokitansky–Aschoff sinuses, and serosal versus hepatic surface involvement.

Minimum 3 sections

Complete sampling if dysplasia, etc.

Extensive sampling if cancer

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Did I miss anything?

- For simple cholecystectomy, is laparoscopic cholecystectomy feasible?
  - Japanese Society of HBP Surgery recommends open cholecystectomy
    - Port site recurrence?
  - Accumulating evidence for laparoscopy
    - Comparable outcome in colon cancer, gastric cancer, thyroid cancer, etc.
    - Most of incidental early GB cancers are found after laparoscopic cholecystectomy and display acceptable long-term outcomes
    - MIS shows promising results even in advanced GB cancer

Medicine
OBSERVATIONAL STUDY

OPEN

Impact of Type of Surgery on Survival Outcome in Patients With Early Gallbladder Cancer in the Era of Minimally Invasive Surgery

Oncologic Safety of Laparoscopic Surgery

Jin-Young Jang, MD, PhD, Jin Seok Heo, MD, PhD, Youngmin Han, BS, Jihoon Chang, MD, MS, Jae Ri Kim, MD, Hongbeom Kim, MD, MS, Wooil Kwon, MD, PhD, Sun-Whe Kim, MD, PhD, Seong Ho Choi, MD, PhD, Dong Wook Choi, MD, PhD, Kyoungbun Lee, MD, PhD, Kee-Taek Jang, MD, PhD, Sung-Sik Han, MD, PhD, and Sang-Jae Park, MD, PhD

TABLE 3. Patients Characteristics (Unadjusted and Propensity Score [PS] Matched Between Laparoscopic and Open Surgery

	Before PS Matching			After PS Matching		
Variable	**Laparoscopic (n = 94)**	**Open (n = 103)**	***P* Value**	**Laparoscopic (n = 61)**	**Open (n = 61)**	***P* Value**
Demographics						
Age	63.8 ± 10.9	63.1 ± 10.4	0.643	63.3 ± 10	62.2 ± 10	0.583
Sex (M:F)	31:63	54:49	0.006	28:33	27:34	0.317
ASA (1/2/3)	39/47/8	40/55/8	0.892	17/38/6	24/33/4	0.079
Symptom	37 (39.4%)	63 (61.2%)	0.002	23 (37.7%)	32 (52.5%)	0.117
Combined GB Stone	25 (26.6%)	27 (26.2%)	0.632	18 (29.5%)	16 (26.7%)	0.706
Perioperative finding						
Operation time	65.2 ± 42.3	197.0 ± 81.7	<0.001	66.9 ± 46.5	187.7 ± 87.1	<0.001
Estimated blood loss	31.7 ± 64.3	319.6 ± 270.6	<0.001	35.4 ± 78.0	326.7 ± 299.5	<0.001
Postop hospital stay	2.3 ± 2.0	9.2 ± 5.3	<0.001	2.4 ± 2.3	8.7 ± 4.9	<0.001
Complication	1 (1.1%)	4 (3.9%)	0.371	0 (0.0%)	1 (1.6%)	0.317
Adjuvant Chemo Tx.	0 (0.0%)	6 (5.8%)	0.030	0 (0.0%)	3 (4.9%)	0.083
Pathologic finding						
T stage						
T1a	77 (81.9%)	48 (46.6%)	<0.001	44 (72.1%)	43 (70.5%)	0.317
T1b	17 (18.1%)	55 (53.4%)		17 (27.9%)	18 (29.5%)	
N stage						
N0	35 (37.2%)	84 (81.6%)	<0.001	23 (37.7%)	48 (78.7%)	<0.001
N1	0 (0.0%)	4 (3.9%)		0 (0.0%)	1 (1.6%)	
NX	59 (62.8%)	15 (14.6%)		38 (62.3%)	12 (19.7%)	
Differentiation			0.011			0.300
Well	76 (89.4%)	62 (72.1%)		49 (90.7%)	45 (81.8%)	
Moderate	8 (9.4%)	19 (22.1%)		4 (7.4%)	7 (12.7%)	
Poorly/undifferentiated	1 (1.2%)	5 (5.8%)		1 (1.9%)	3 (5.5%)	
Follow-up data						
Median follow-up (mo)	57.9 ± 44.9	72.4 ± 44.5		55.0 ± 44.4	76 ± 42.2	
Recurrence	0 (0.0%)	4 (2.0%)	0.123	0 (0.0%)	2 (3.3%)	0.496
5-year survival rate	94.9%	98.8%	0.528	92.7%	100.0%	0.332

ASA = American Society of Anesthesiologists' Physical Status Classification System, PS = propensity score.

Medicine
OBSERVATIONAL STUDY

OPEN

Impact of Type of Surgery on Survival Outcome in Patients With Early Gallbladder Cancer in the Era of Minimally Invasive Surgery

Oncologic Safety of Laparoscopic Surgery

Jin-Young Jang, MD, PhD, Jin Seok Heo, MD, PhD, Youngmin Han, BS, Jihoon Chang, MD, MS, Jae Ri Kim, MD, Hongbeom Kim, MD, MS, Wooil Kwon, MD, PhD, Sun-Whe Kim, MD, PhD, Seong Ho Choi, MD, PhD, Dong Wook Choi, MD, PhD, Kyoungbun Lee, MD, PhD, Kee-Taek Jang, MD, PhD, Sung-Sik Han, MD, PhD, and Sang-Jae Park, MD, PhD

Abstract: Laparoscopic surgery has been widely accepted as a feasible and safe treatment modality in many cancers of the gastrointestinal tract. However, most guidelines on gallbladder cancer (GBC) regard laparoscopic surgery as a contraindication, even for early GBC. This study aims to evaluate and compare recent surgical outcomes of laparoscopic and open surgery for T1(a,b) GBC and to determine the optimal surgical strategy for T1 GBC.

The study enrolled 197 patients with histopathologically proven T1 were investigated.

Of the 197 patients, 116 (58.9%) underwent simple cholecystectomy, including 31 (15.7%) who underwent open cholecystectomy and 85 (43.1%) laparoscopic cholecystectomy. The remaining 81 (41.1%) patients underwent extended cholecystectomy. Five-year disease-specific survival rates were similar in patients who underwent simple and extended cholecystectomy (96.7% vs 100%, $P = 0.483$), as well as being similar in patients in the simple cholecystectomy group who underwent open and laparoscopic cholecystectomy (100% vs 97.6%, $P = 0.543$). Type of surgery had no effect on recurrence patterns.

Laparoscopic cholecystectomy for T1 gallbladder cancer can provide similar survival outcomes compared to open surgery. Considering less blood loss and shorter hospital stay with better cosmetic outcome, laparoscopic cholecystectomy can be justified as a standard treatment for T1b as well as T1a gallbladder cancer when done by well-experienced surgeons based on exact pathologic diagnosis.

Not conclusive, but MIS is likely to expand in GB cancers, especially in early GB cancers.

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Early Gallbladder (GB) Cancer

- The definition of early GB cancer
  - T1 GB cancer?
  - GB cancer confined to the GB?

T stage	
T1 T1a T1b	Tumor invades the lamina propria or muscular layer Tumor invades the lamina propria Tumor invades the muscular layer
T2	Tumor invades perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum) Or the tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

T2 GB cancer

- T2a
  - Tumor invades perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)

- T2b
  - Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver

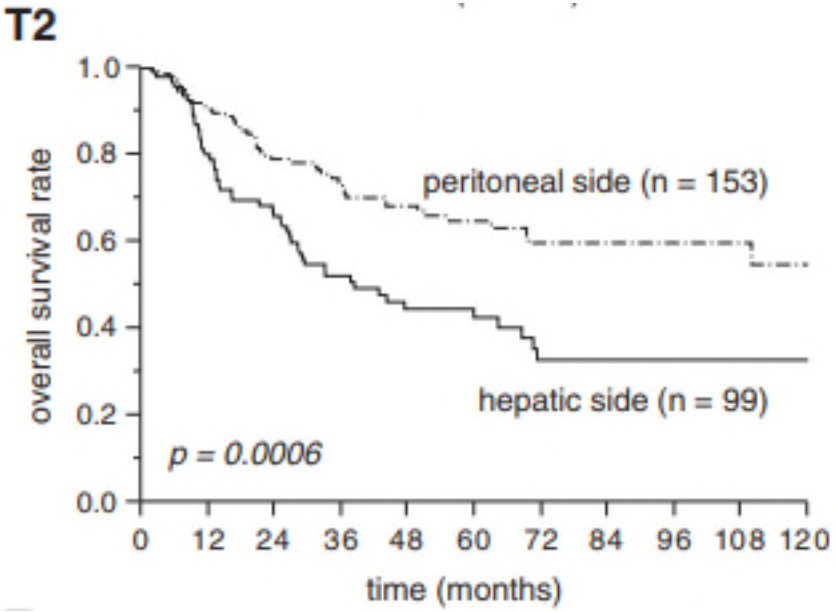
T2 GB cancer

ORIGINAL ARTICLE

Tumor Location Is a Strong Predictor of Tumor Progression and Survival in T2 Gallbladder Cancer

An International Multicenter Study

Junichi Shindoh, MD, PhD,† Xabier de Aretxabala, MD,‡ Thomas A. Aloia, MD,* Juan Carlos Roa, MD, MSc,§ Ivan Roa, MD,‖ Giuseppe Zimmitti, MD,*¶ Milind Javle, MD,** Claudius Conrad, MD, PhD,* Dipen M. Maru, MD,†† Taku Aoki, MD, PhD,† Luca Vigano, MD,¶ Dario Ribero, MD,¶ Norihiro Kokudo, MD, PhD,† Lorenzo Capussotti, MD,¶ and Jean-Nicolas Vauthey, MD**



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T2 GB cancer

- Traditionally, T2 GB cancer surgical extent is recommended as;

Cholecystectomy + LN dissention
+ **liver resection**

T2 GB cancer

ORIGINAL ARTICLE

Gut and Liver, Vol. 10, No. 1, January 2016, pp. 140-146

Effects of Surgical Methods and Tumor Location on Survival and Recurrence Patterns after Curative Resection in Patients with T2 Gallbladder Cancer

Woohyun Jung, Jin-Young Jang, Mee Joo Kang, Ye Rim Chang, Yong Chan Shin, Jihoon Chang, and Sun-Whe Kim

Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

LN metastasis was the most important prognostic factor in patients curatively resected for T2 GB cancer, with extended cholecystectomy tending to improve 5-year DFS rate. Tumor location did not affect survival outcome or recurrence patterns. However, no patient with serosal side tumors experienced GB bed or liver recurrence even after SC.

EC is the preferred surgical treatment for T2 GB cancer overall; however, the rarity of GB bed recurrence in patients with serosal side T2 GB cancer suggests that SC with regional LN dissection may be sufficient for these patients, if curative resection could be achieved.

Ann Surg Oncol (2015) 22:2779–2786
DOI 10.1245/s10434-014-4300-7

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Surgical Strategy for T2 Gallbladder Cancer According to Tumor Location

Huisong Lee, MD[1], Dong Wook Choi, MD, PhD[1], Jin Young Park, MD[1], Sangmin Youn, MD[1], Wooil Kwon, MD[1], Jin Seok Heo, MD, PhD[1], Seong Ho Choi, MD, PhD[1], and Kee-Taek Jang, MD, PhD[2]

[1]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

CONCLUSIONS

Tumor location was an important factor associated with survival and should be considered when determining the required extent of surgery. If T2 gallbladder cancer is located on the peritoneal side and there is no invasion to the hepatic side and no evidence of LN metastasis, hepatic resection is not always necessary.

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Oncologic outcome of T2 gallbladder cancer and the optimal surgical treatment

Korean multi-institutional analysis

- **Aim**
  - **To re-investigate whether extended cholecystectomy is the treatment of choice**

Materials and methods

- Period: 1987 to 2014
- Subjects: 577 patients operated for T2 GB cancer
- Participated tertiary institutions

Seoul National University Hospital (n=283)
National Cancer Center (n=67)
Samsung Medical Center (n=227)

- Survival data and recurrence data
- Demographics
- Pathology report review
- CT review

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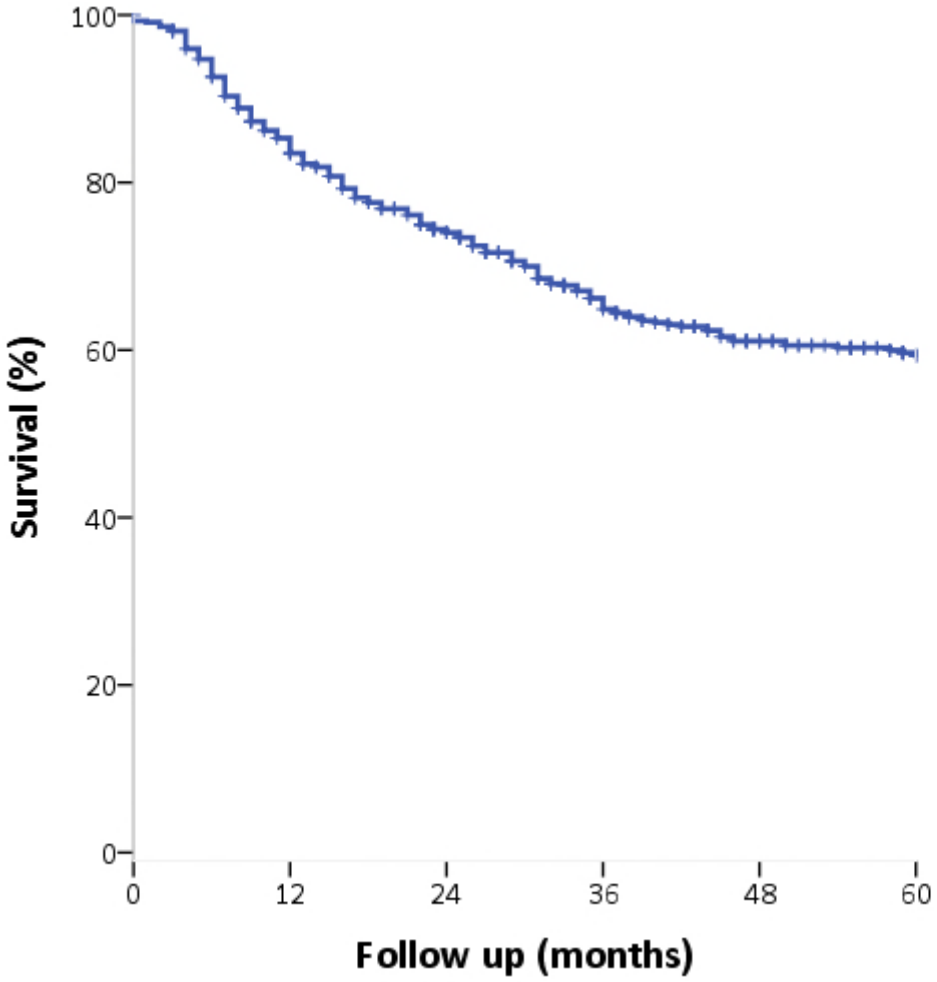
Overall survival



N=577
Median 121 month
5YSR 59.4%

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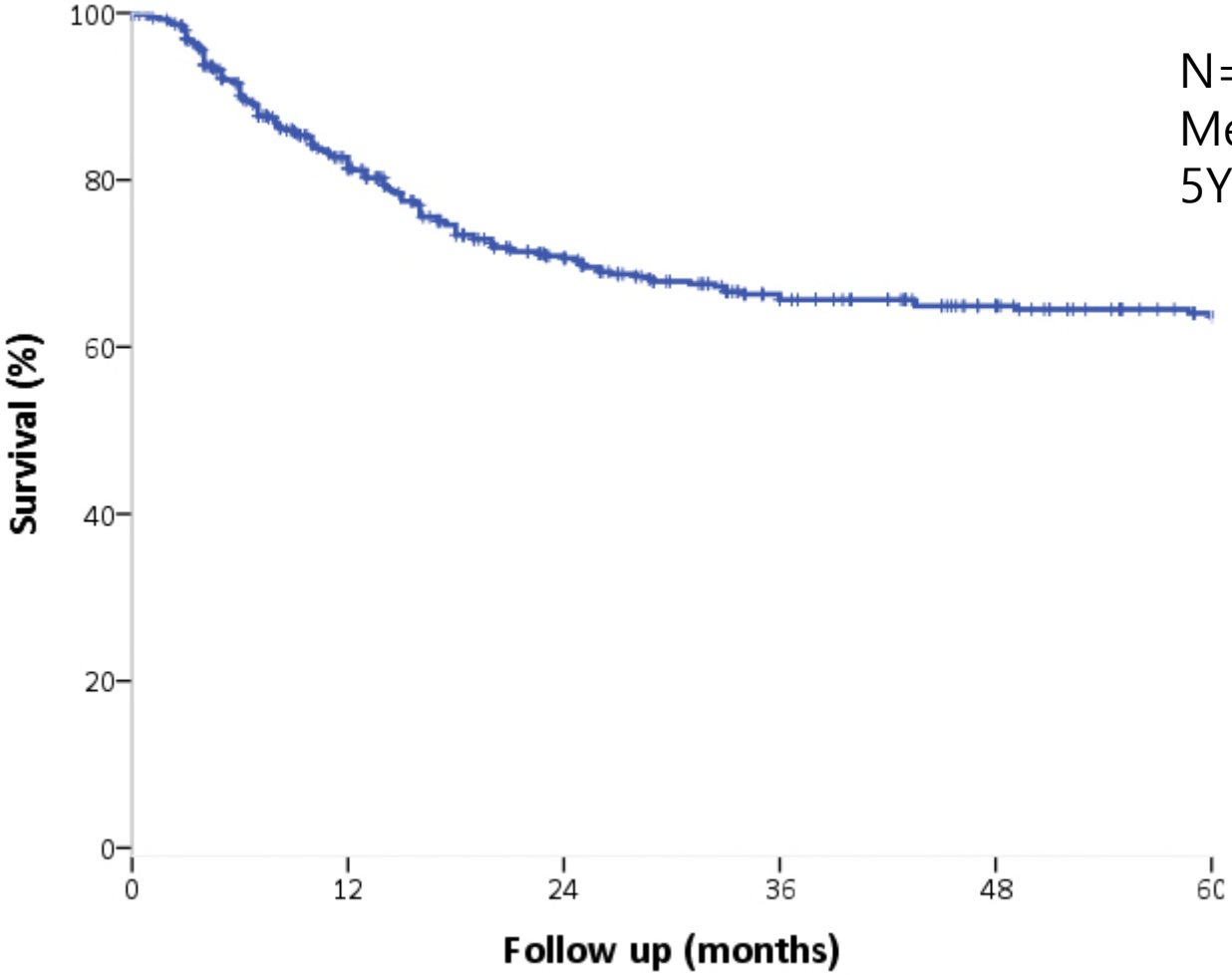
Disease free survival



N=577
Median not reached
5YDFSR 63.6%

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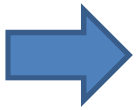
Location and operation types

- Subgroup analysis with curatively treated patients
- T2 GB cancer patients exclusive of;
  - R2 resection
  - N2 (periaortic, pericaval, SMA, celiac artery LN)
  - M1
  - Incomplete information on location

500 patients
Seoul National University Hospital (n=222)
National Cancer Center (n=59)
Samsung Medical Center (n=219)

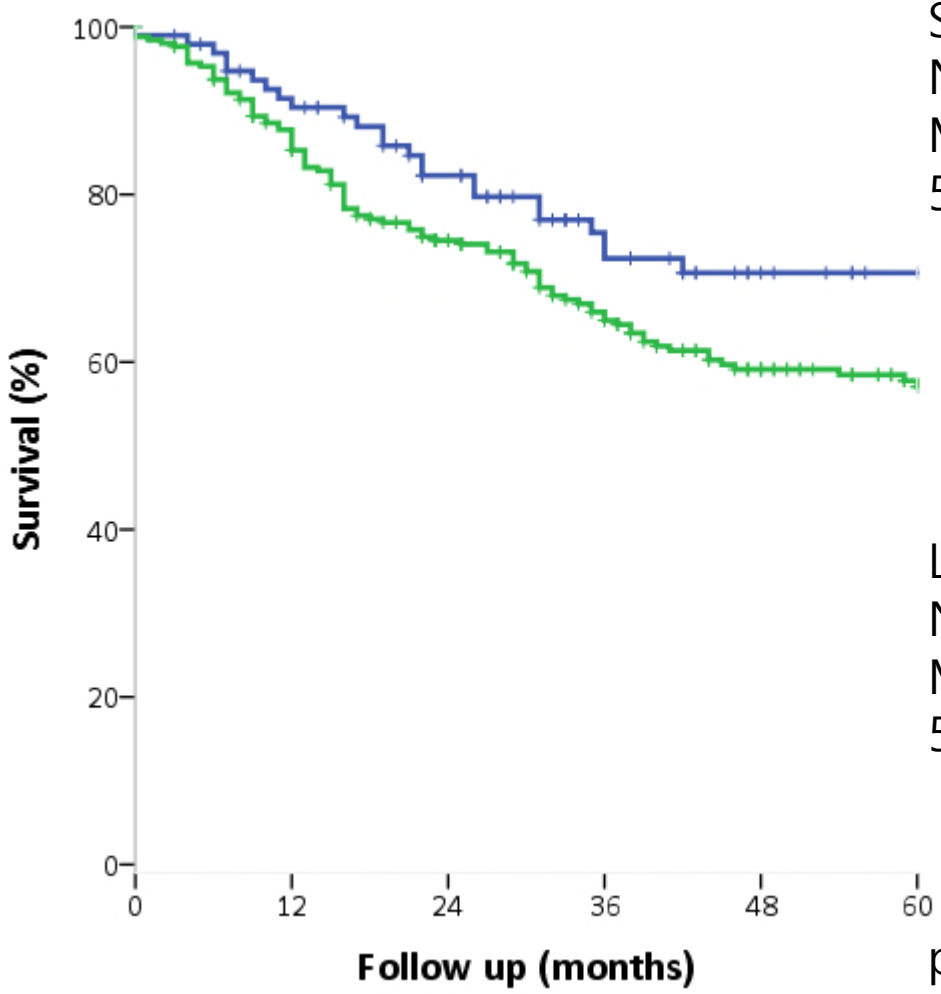
Propensity Score Matching

- Simple cholecystectomy group
  - Older patients (68.7 ± 10.1 vs. 62.4 ± 10.4, p<0.001)
  - Higher ASA score (p<0.001)



Corrected for age and ASA score using 1:2 propensity score matching

Overall survival – location



Serosal side
N=99
Median NA
5YSR 70.6%

Liver side
N=258
Median 90 month
5YSR 57.0%

p=0.102

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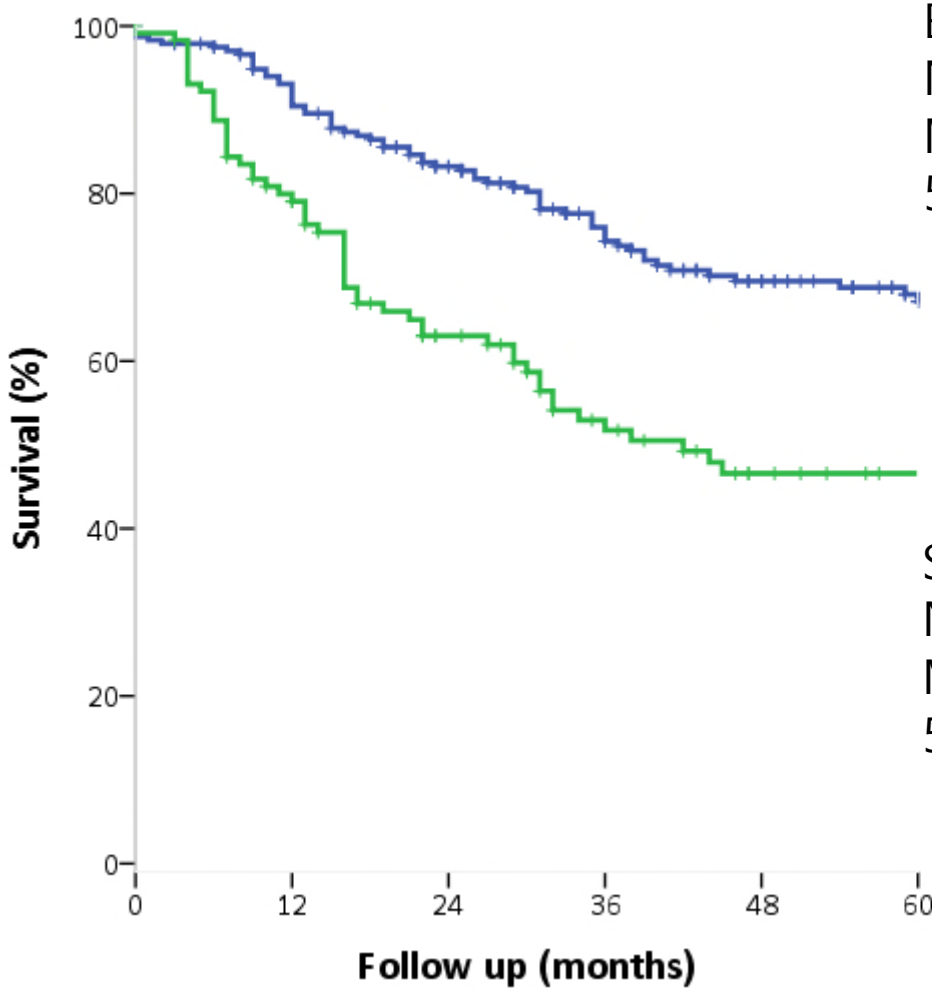
Overall survival – op type



EC
N=239
Median 167month
5YSR 67.1%

SC
N=118
Median 42 month
5YSR 46.6%

P<0.001

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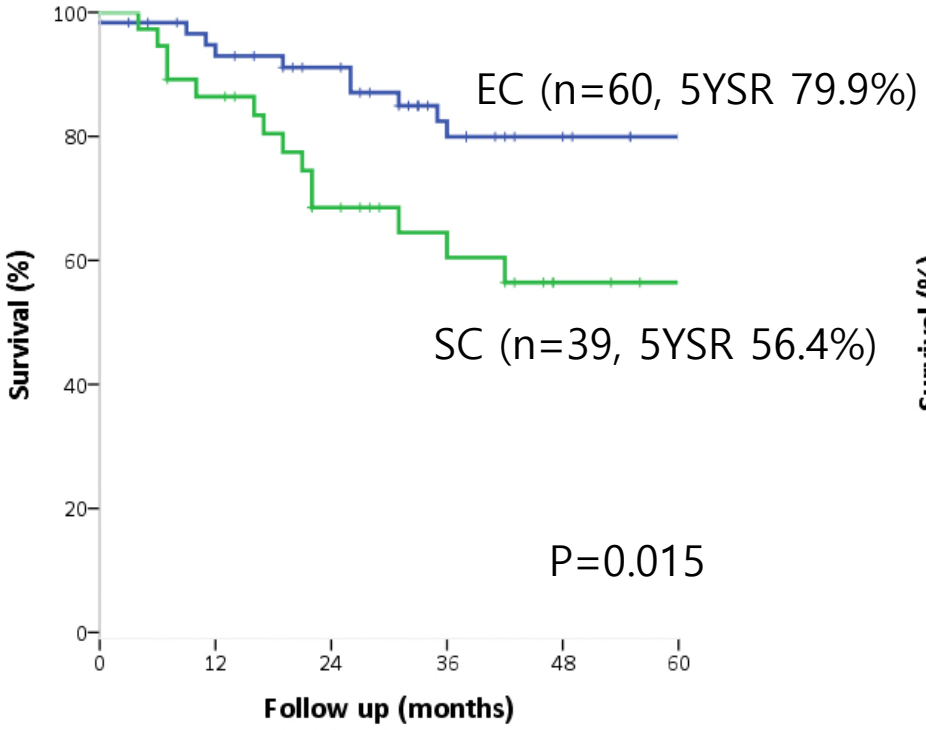
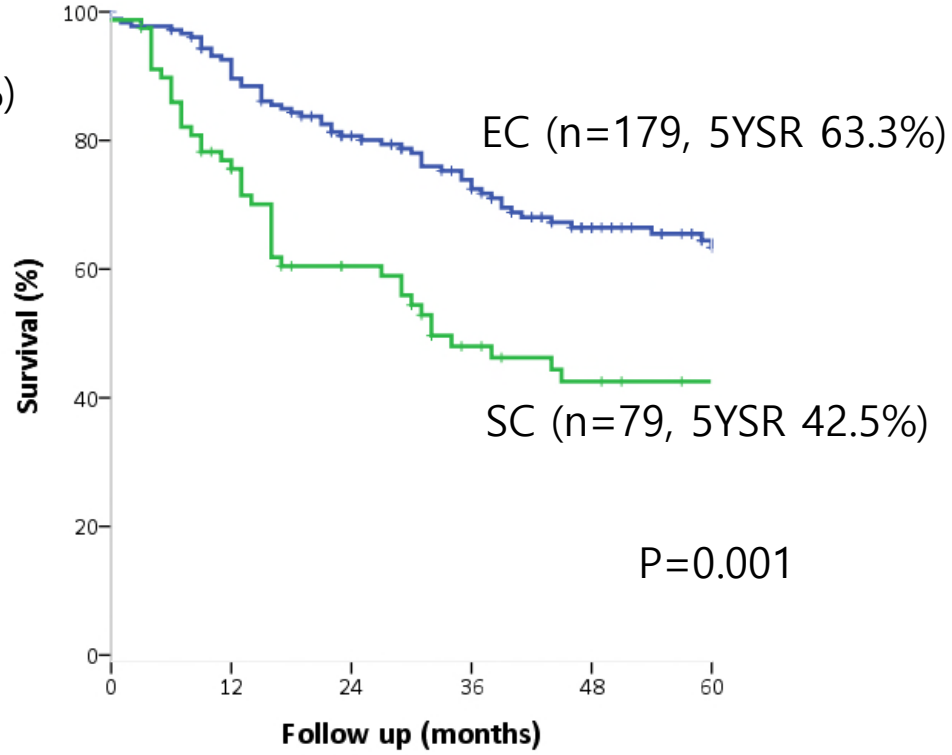
Overall survival – location & op



Serosal



Liver

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Conclusion

- **Extended cholecystectomy** offers better survival outcome compared to simple cholecystectomy regardless of location of tumor

Extended cholecystectomy should be performed for T2 GB cancer whenever the patients' physical condition permits regardless of the location of tumor

Take home message

(based on our studies)

- **Extent of Surgery in early GB cancer**
  - T1a
    - Simple cholecystectomy
    - Laparoscopic cholecystectomy likely to be feasible
  - T1b
    - Simple cholecystectomy, most likely
    - Laparoscopic cholecystectomy likely to be feasible
  - T2a
    - Extended cholecystectomy
  - T2b
    - Extended cholecystectomy

Future directions

- Standardization of surgical techniques
- Standardization of pathologic examinations

- Additional large-scale cohort studies using more standardized systems
  - surgical extent
  - method

To establish evidence-based guidelines for the treatment of GB cancer


Thank You!