Neoadjuvant/adjuvant treatment in cholangiocarcinoma

Marc De Man

Digestieve Oncologie

UZ Gent

Outline

- Adjuvant treatment
- Neoadjuvant treatment
- Future directions
- Conclusions

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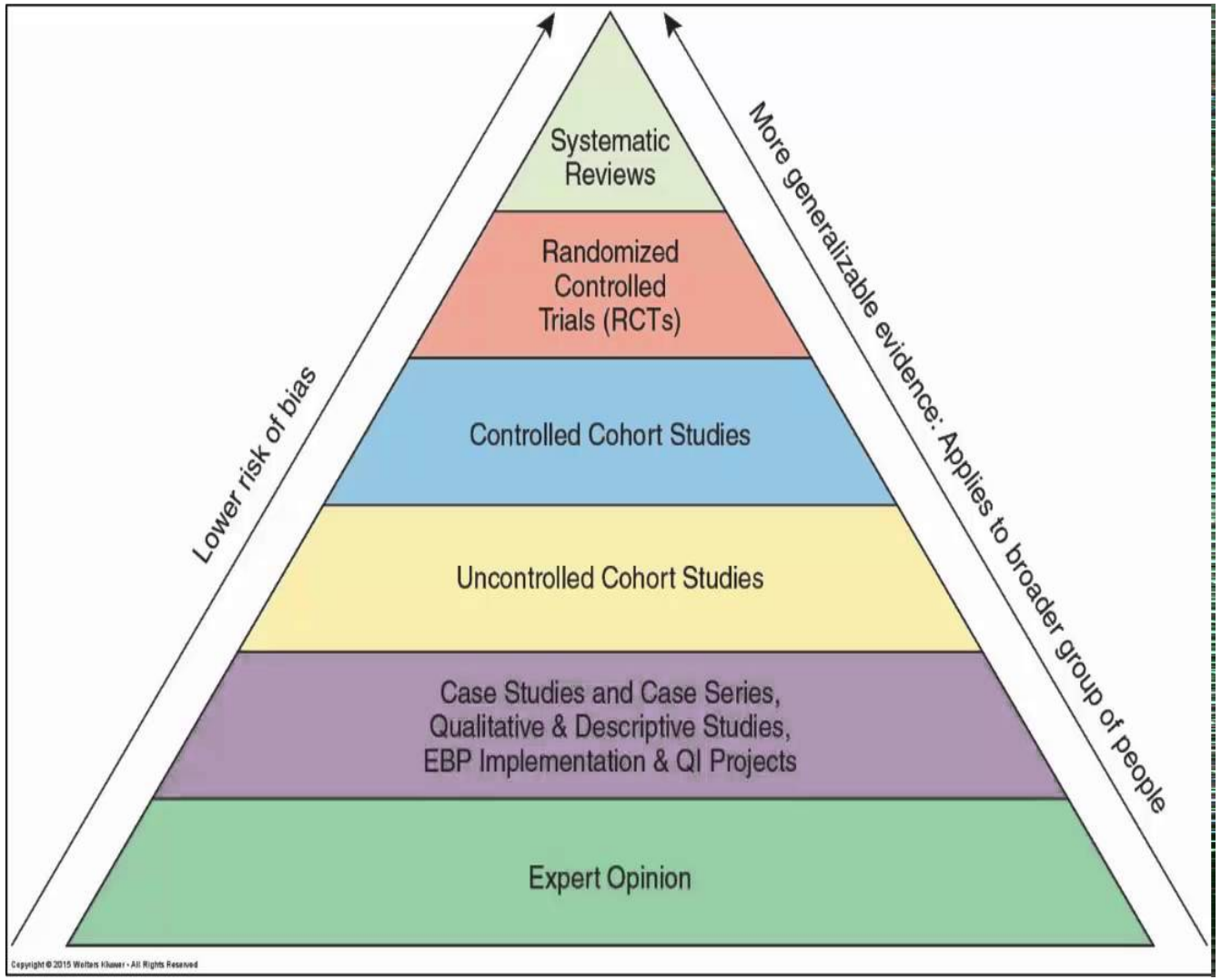

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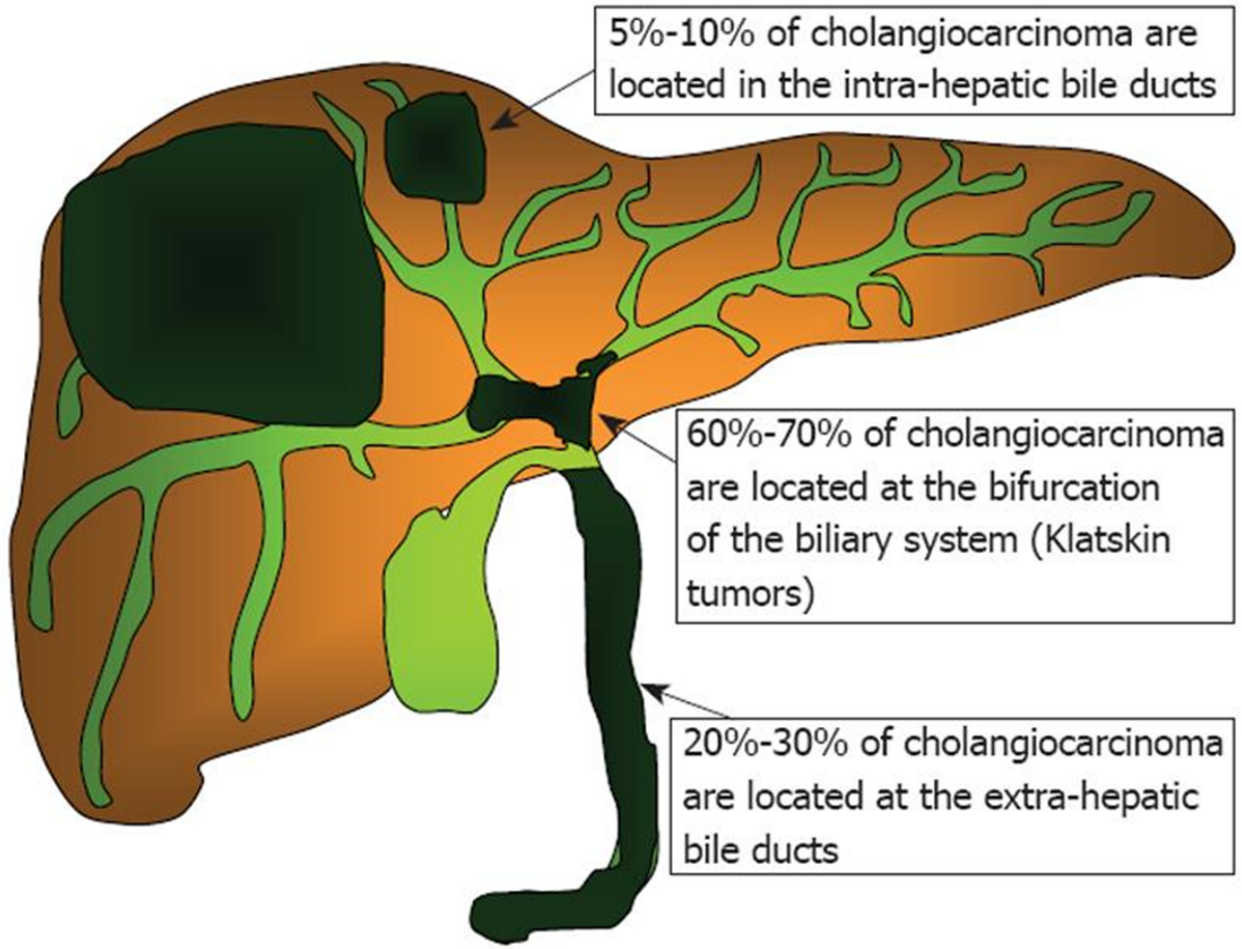
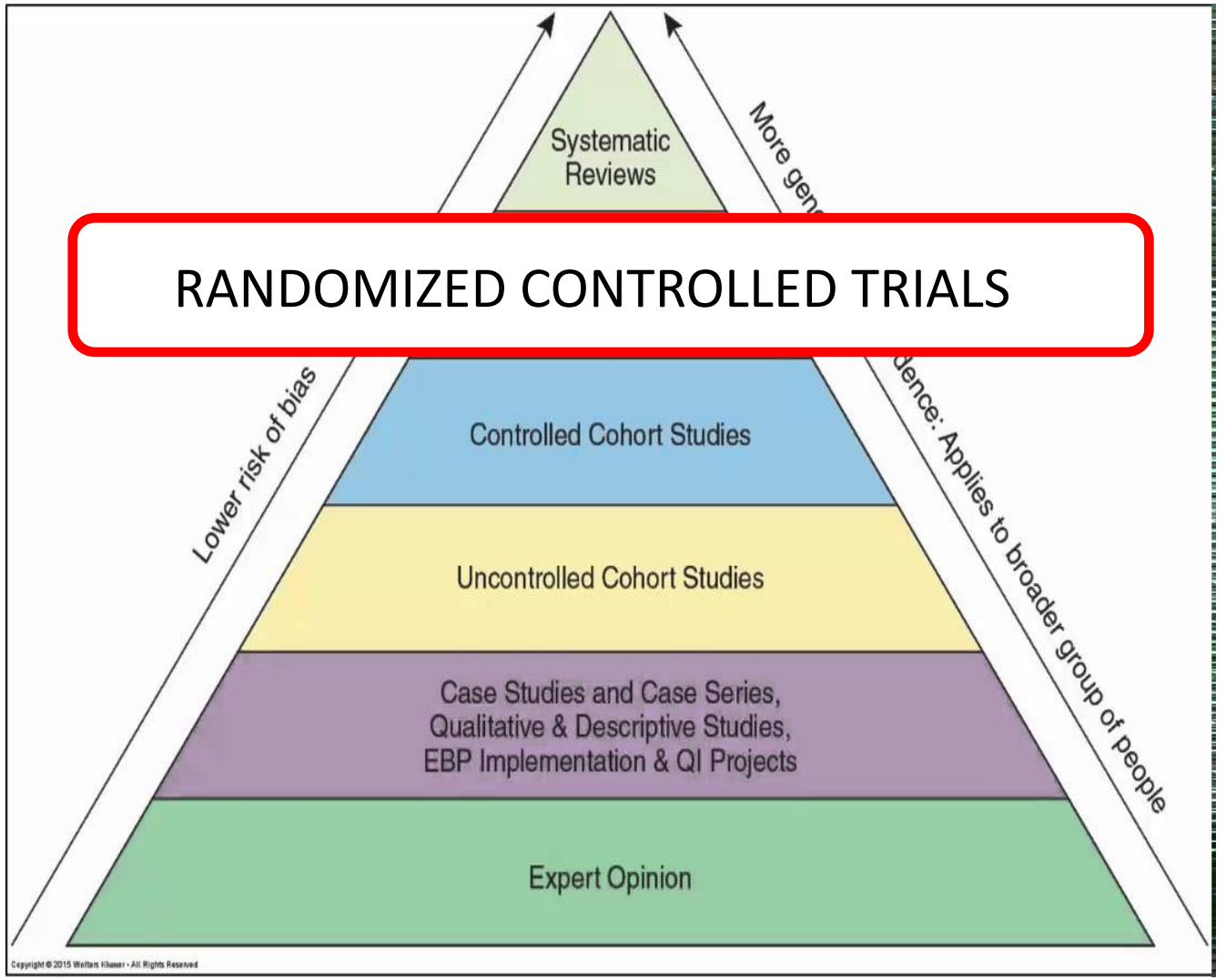


Multidisciplinary Team Discussion

Outline

- **Adjuvant treatment**
- **Neoadjuvant treatment**
- **Future directions**
- **Conclusions**



Adjuvant treatment : meta-analysis 2012

study	design	Number pt	Tumor	R1 (%)	LN + (%)	OS		p	year
						S	S +CT		
Horgan	Meta-analyse	(6712)	EHCC IHCC			OR 0.39, 95% CI 0.23-0.66		<0,001	2012
						S	S +RCT		
						OR 0.61, 95% CI 0,38-0,99		<0,049	2012

after exclusion of 2 registry analyses, a significant benefit for adjuvant treatment over observation alone was demonstrated

The greatest benefit :
LN+
R1 resection.

Horgan AM, J Clin Oncol. 2012.

Adjuvant treatment : 2016

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

The high rates of local and distant recurrence following surgery justify the consideration of an adjuvant treatment.

The results of two phase III studies that have completed accrual and are **awaiting maturation of data [BilCap (observation versus adjuvant capecitabine; UK, NCT00363584) and Prodige-12 (observation versus gemcitabine/oxaliplatin; France, NCT01313377)]** are awaited and are likely to define future adjuvant strategies. A further study [**ACTICCA-1 (observation versus cisplatin/gemcitabine; Germany, NCT02170090**)] is open and recruiting patients

Adjuvant treatment : BCAT trial

study	design	Number pt	Exp treatment	R1 (%)	LN + (%)	OS		p	year
						S	S +CT		
Horgan	Meta-analyse	6712	chemotherapy			OR 0.39, 95% CI 0.23-0.66		<0,001	2012
BCAT	**RCT**	**225**	**GEM**			**63,8 M**	**62,3 M**	**0,964**	**2018**

Adjuvant treatment : PRODIGE 12 TRIAL

study	design	Number pt	Exp treatment	R1 (%)	LN + (%)	OS		p	year
						S	S +CT		
Horgan	Meta-analyse	6712	chemotherapy			OR 0.39, 95% CI 0.23-0.66		<0,001	2012
BCAT	RCT	225	GEM			63,8 M	62,3 M	0,964	2018
PRODIGE 12	**RCT**	**193**	**GEM + OXALI**	**13**	**33**	**50,8 M**	**75,8 M**	**0,74**	**2019**

SUR ⟷ SUR + CT

Adjuvant treatment : PRODIGE 12 TRIAL

study	design	Number pt	Exp treatment	R1 (%)	LN + (%)	OS		p	year
						S	S +CT		
Horgan	Meta-analyse	6712	chemotherapy			OR 0.39, 95% CI 0.23-0.66		<0,001	2012
BCAT	RCT	225	GEM			63,8 M	62,3 M	0,964	2018
PRODIGE 12	RCT	193	GEM + OXALI	13	33	50,8 M	75,8 M	0,74	2019
BILCAP	**RCT**	**447**	**CAPECITABINE**	**38 %**	**54 %**	**36 M**	**52 M**	**<0,001**	**2019**

adjusted by prognostic factors (nodal status, grade of disease and gender)

Primrose J; Lancet Oncology 2019

Adjuvant treatment : BILCAP TRIAL

A randomized phase 3 BILCAP trial

- Histologically confirmed biliary tract cancer*;
- Radical and macroscopically complete surgery;
- ECOG PS ≤ 2; (N = 447)

Biliary Tumors

Gall Bladder Carcinoma

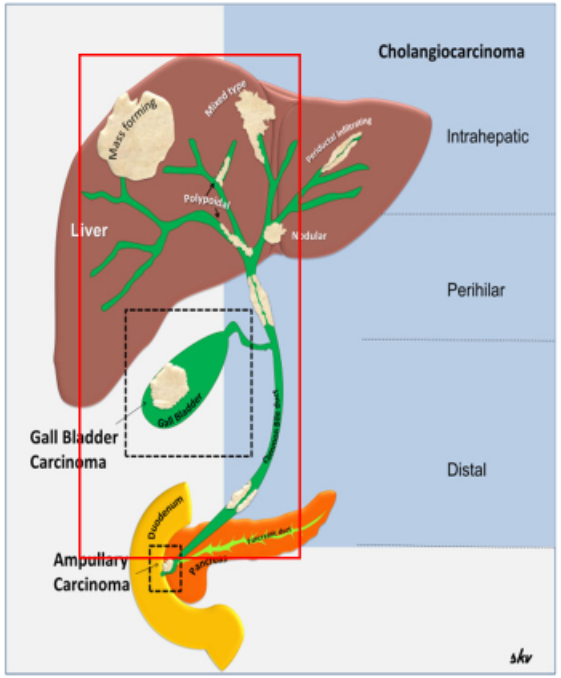
Ampullary Carcinoma

Cholangiocarcinoma

Intrahepatic

Perihilar

Distal



*Included: intrahepatic CC, hilar CC, muscle-invasive gallbladder cancer, and lower common bile duct CC

Excluded: pancreatic, ampullary, mucosal (T1a) gallbladder cancers; incomplete recovery from prior surgery

Primrose J; Lancet Oncology 2019

Adjuvant treatment : BILCAP TRIAL

A randomized phase 3 BILCAP trial

- Histologically confirmed biliary tract cancer*;
- Radical and macroscopically complete surgery;
- ECOG PS ≤ 2; (N = 447)

Stratified by surgical center, R0 vs R1 resection, ECOG PS

447 R

1:1

CAPECITABINE (n=223)

Capecitabine 1250 mg/m^2 BID
Days 1-14 of 21-day cycle for 8 cycles

OBSERVATION (n=224)

. Primary endpoint: OS

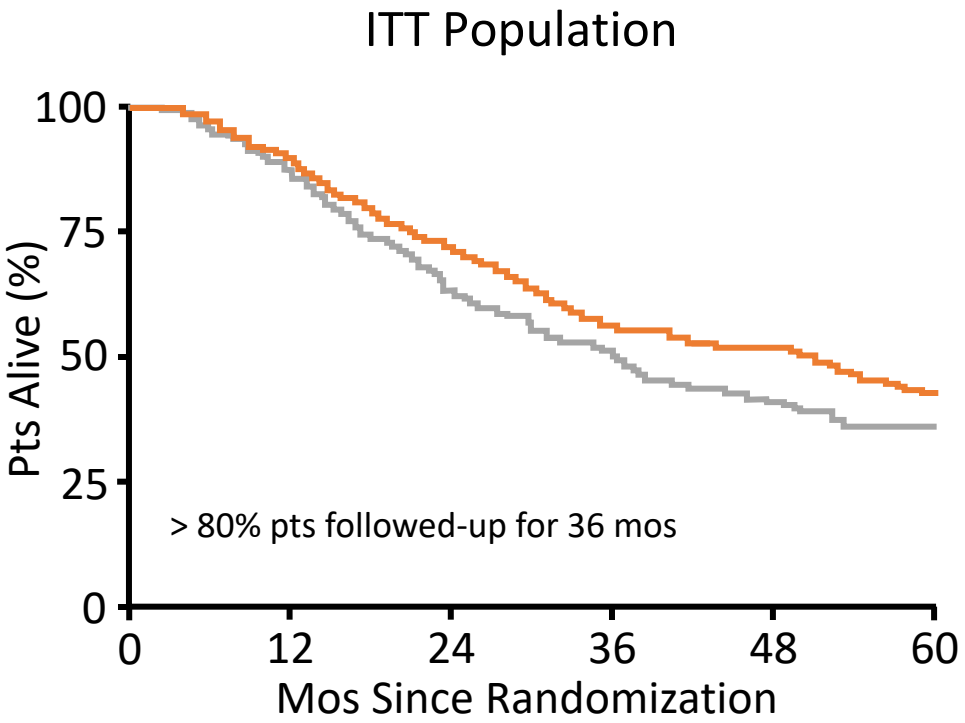
secondary endpoints: RFS

Primrose J; Lancet Oncology 2019

Adjuvant treatment : BILCAP TRIAL

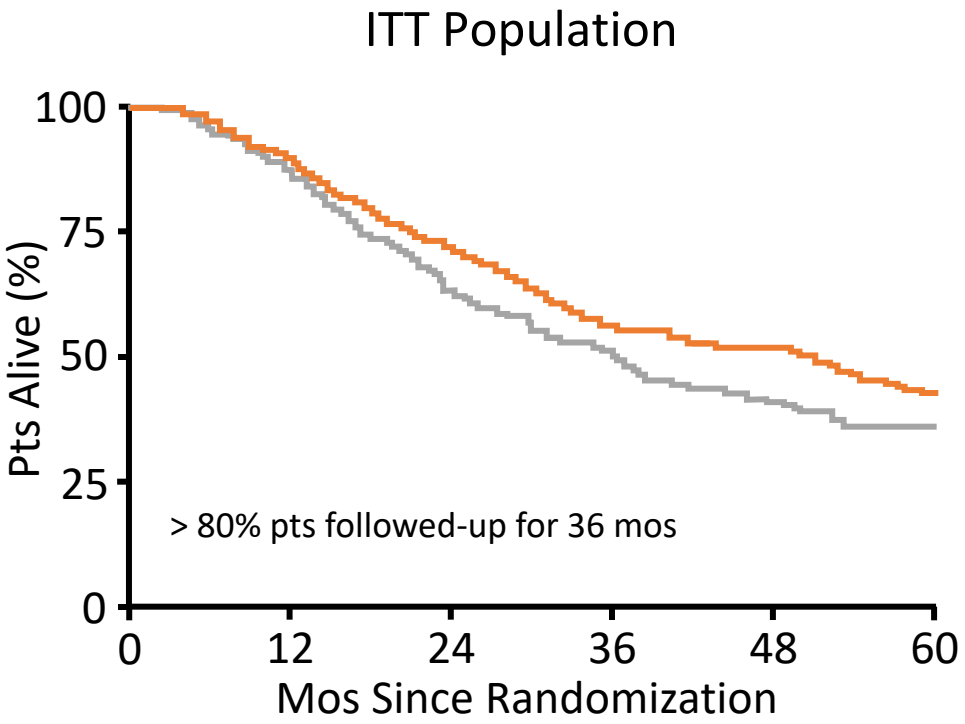
Characteristic, %	Capecitabine Arm (n = 223)	Observation Arm (n = 224)
Male	50	50
Median age, yrs (IQR)	62 (55-68)	64 (55-69)
Tumor site		
▪ Intrahepatic CC	19	18
▪ Hilar CC	29	28
▪ Muscle-invasive gall bladder carcinoma	17	18
Resection status, R0/R1	62/38	63/38
ECOG PS, 0/1/2	5/52/3	45/52/3
Lymph node status, N0/N1/not evaluable	45/48/7	48/46/6

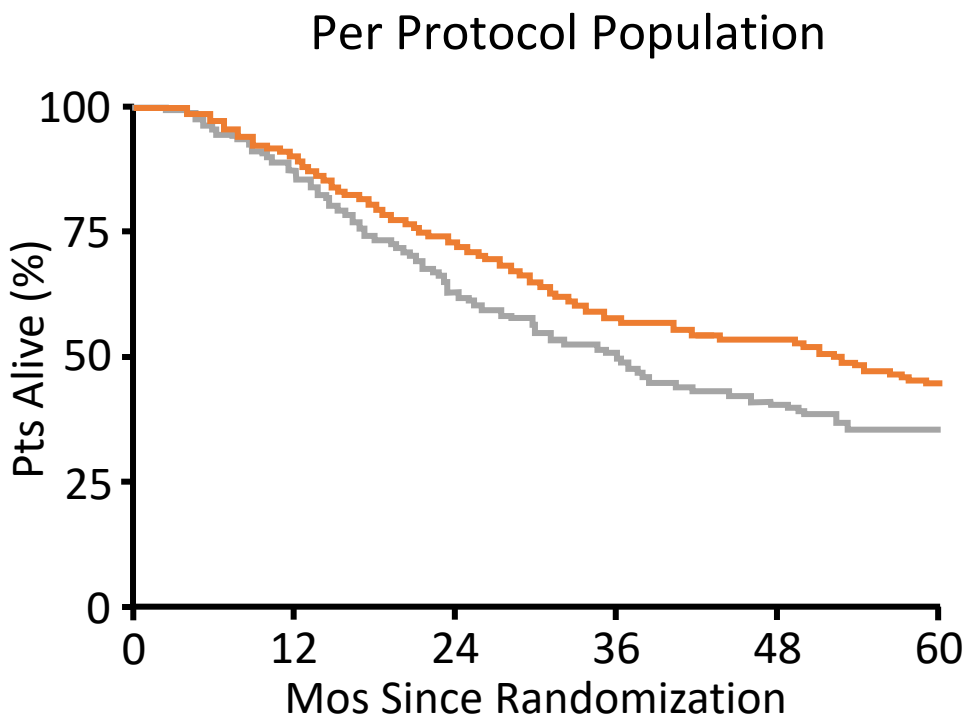
Adjuvant treatment : BILCAP TRIAL OS



Treatment	Median OS, Mos (95% CI)	HR (95% CI)
Capecitabine	51.1 (34.6-59.1)	0.81 (0.63-1.04) *P* = .097
Observation	36.4 (29.7-44.5)	

Adjuvant treatment : BILCAP TRIAL OS





Prespecified sensitivity analyses adjusting for further prognostic factors (gender, nodal status, disease grade) HR 0.70 (95% CI: 0.55-0.91; *P* = .007)

Treatment	Median OS, Mos (95% CI)	HR (95% CI)
Capecitabine	52.7 (40.3-NR)	0.75 (0.58-0.97) *P* = .028
Observation	36.1 (29.6-44.2)	

Adjuvant treatment : BILCAP TRIAL Safety and QoL

- Safety population included 213 patients who received capecitabine

Adverse Event, n (%)	All Grades	Grades 1/2	Grades 3/4
Fatigue	175 (82)	159 (75)	16 (8)
Plantar-palmar erythema	174 (82)	130 (61)	44 (21)
Diarrhea	137 (64)	121 (57)	16 (8)
Nausea	108 (51)	106 (50)	2 (1)
Mucositis/stomatitis	96 (45)	94 (44)	2 (1)
Vomiting	50 (24)	49 (23)	1 (0.5)
Neutropenia	49 (23)	45 (21)	4 (2)
Hyperbilirubinemia	45 (21)	42 (20)	3 (1)
Thrombocytopenia	26 (12)	25 (12)	1 (0.5)
Alopecia	20 (9)	20 (9)	0 (0)

QoL was not reduced in capecitabine arm compared with placebo

Screening for DPD deficiency

Primrose J; Lancet Oncology 2019

Adjuvant Therapy for Resected Biliary Tract Cancer: ASCO Clinical Practice Guideline

Rachna T. Shroff, MD[1]; Erin B. Kennedy, MHSc[2]; Melinda Bachini[3]; Tanios Bekaii-Saab, MD[4]; Christopher Crane, MD[5]; Julien Edeline, MD, PhD[6]; Anthony El-Khoueiry, MD[7]; Mary Feng, MD[8]; Matthew H.G. Katz, MD[9]; John Primrose, MD[10]; Heloisa P. Soares, MD, PhD[11]; Juan Valle, MD[12]; and Shishir K. Maithel, MD[13]

Recommendation 1
Patients with resected biliary tract cancer should be offered adjuvant capecitabine chemotherapy for a duration of 6 months (Type: Evidence-based; Benefits outweigh harms;
Evidence quality: Intermediate;
Strength of recommendation: Moderate).

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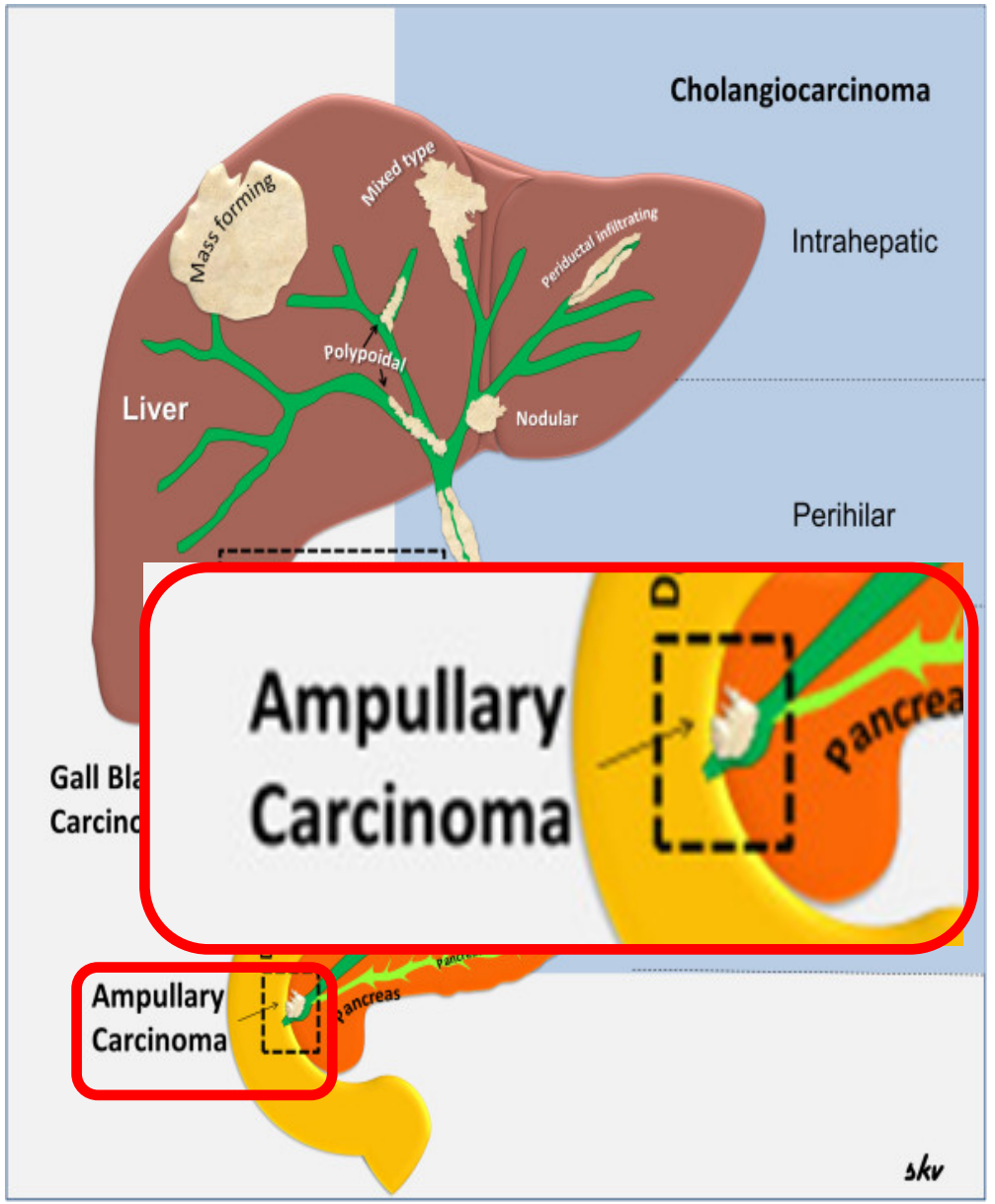
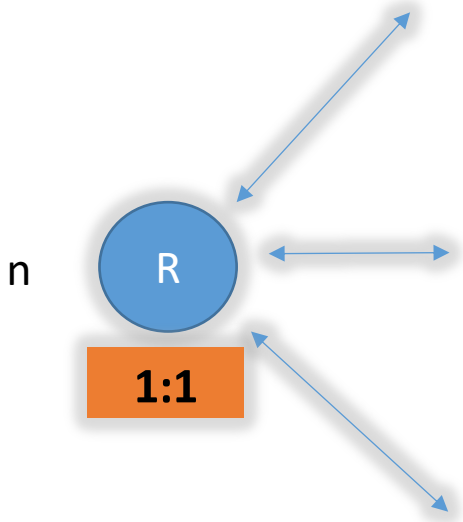


Adjuvant treatment : ESPAC-3 trial

A randomized phase 3 ESPAC-3 trial

- nonpancreatic ductal periampullary adenocarcinoma
- complete macroscopic (R0 or R1) resection



Fluorouracil plus folinic acid (n= 143)

Gemcitabine (n= 141)

Observation (n= 144)

. Primary endpoint: overall survival

secondary endpoints: toxic effects, progression-free survival, and quality of life (QOL).

Adjuvant treatment : ESPAC-3 trial

OVERALL SURVIVAL			HR P
Observation	**Chemotherapy**		
35.2 months CI, 27.2 - 43.0	**43.1 months** CI, 34.0 - 56.0		**HR, 0.86** ***P* = .25**
	5FU	**Gemcitabine**	
	38.9 months	**45.7 months**	**HR, 0.86** **- *P* = .25**

Adjuvant treatment : ESPAC-3 trial

OVERALL SURVIVAL		HR P
Observation	**Chemotherapy**	
35.2 months CI, 27.2 - 43.0	**43.1 months** CI, 34.0 - 56.0	HR, 0,75 P= ,03
	After adjustment for independent prognostic variables of age, bile duct cancer, poor tumor differentiation, and positive lymph nodes and after multiple regression analysis	

Patients in treatment arm had lower quality of life

Adjuvant treatment CCA

Adjuvant treatment should be offered to patients after resection of CCA

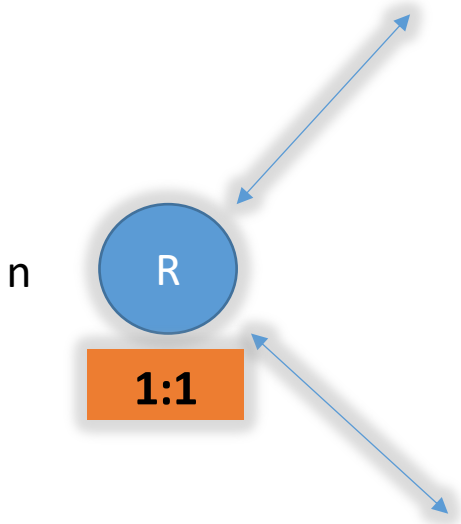
For ampullary adenocarcinoma we have less evidence than for the other localizations

Discussion with patiënt balancing risk of recurrence, potential benefits and side effects of treatment

Adjuvant treatment : ACTICCA-1 TRIAL

A randomized phase trial

- Histologically confirmed biliary tract cancer*;
- Radical and macroscopically complete surgery;
- ECOG PS ≤ 2; (N = 447)



Gemcitabine + Cisplatin
(n=)

Observation
(n=)

Stein A; BMC Cancer, 2015.

. Primary endpoint: DFS

Secondary endpoints: OS, safety and tolerability of chemotherapy, quality of life, and patterns of disease recurrence

Histologically confirmed BTC (intrahepatic, hilar or distal CCA, or muscle invasive GBCA).

Adjuvant treatment : ACTICCA-1 TRIAL

A randomized phase trial

- Histologically confirmed biliary tract cancer*;
- Radical and macroscopically complete surgery;
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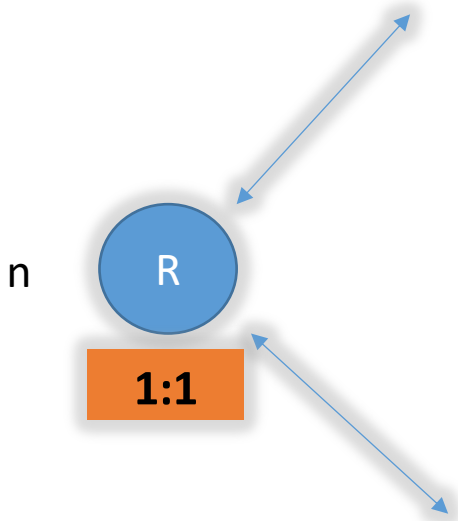

Gemcitabine + Cisplatin
(n=)

Capecitabine
(n=)

. Primary endpoint: DFS

Secondary endpoints: OS, safety and tolerability of chemotherapy, quality of life, and patterns of disease recurrence

After presentation of BILCAP results trial was amended and Capecitabine became controle arm

Stein A; BMC Cancer, 2015.

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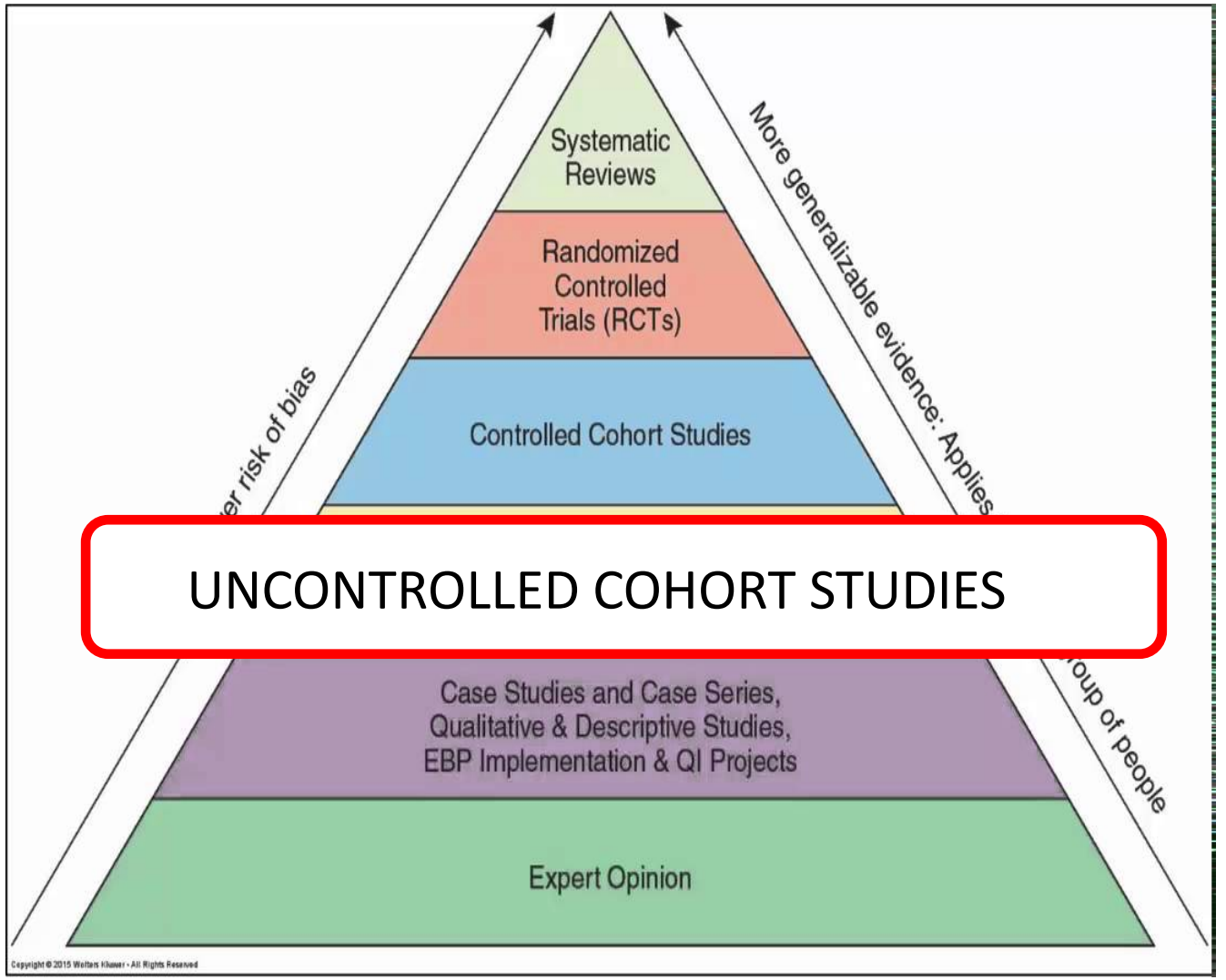

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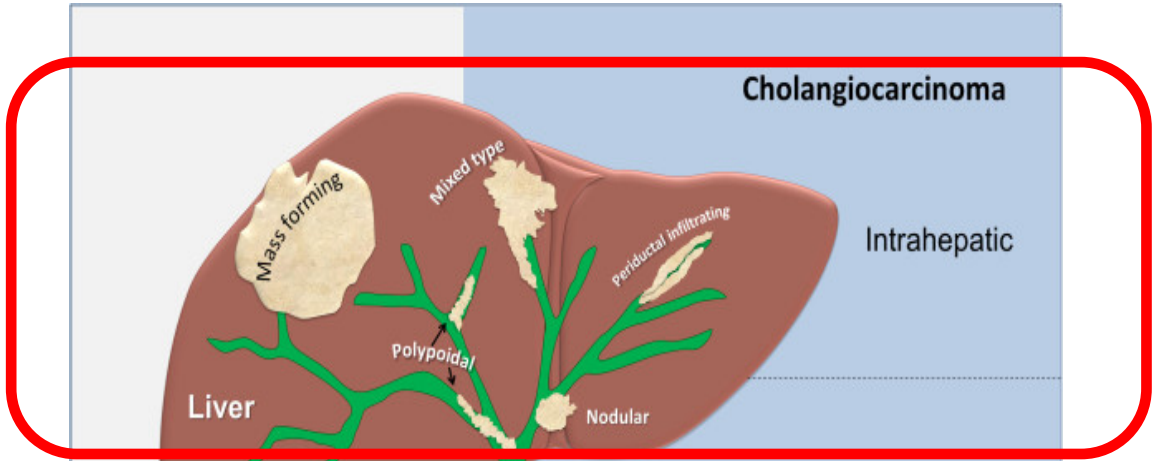
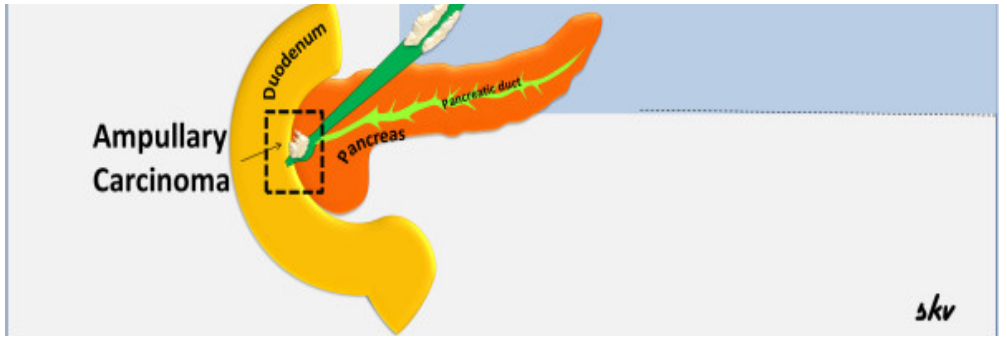
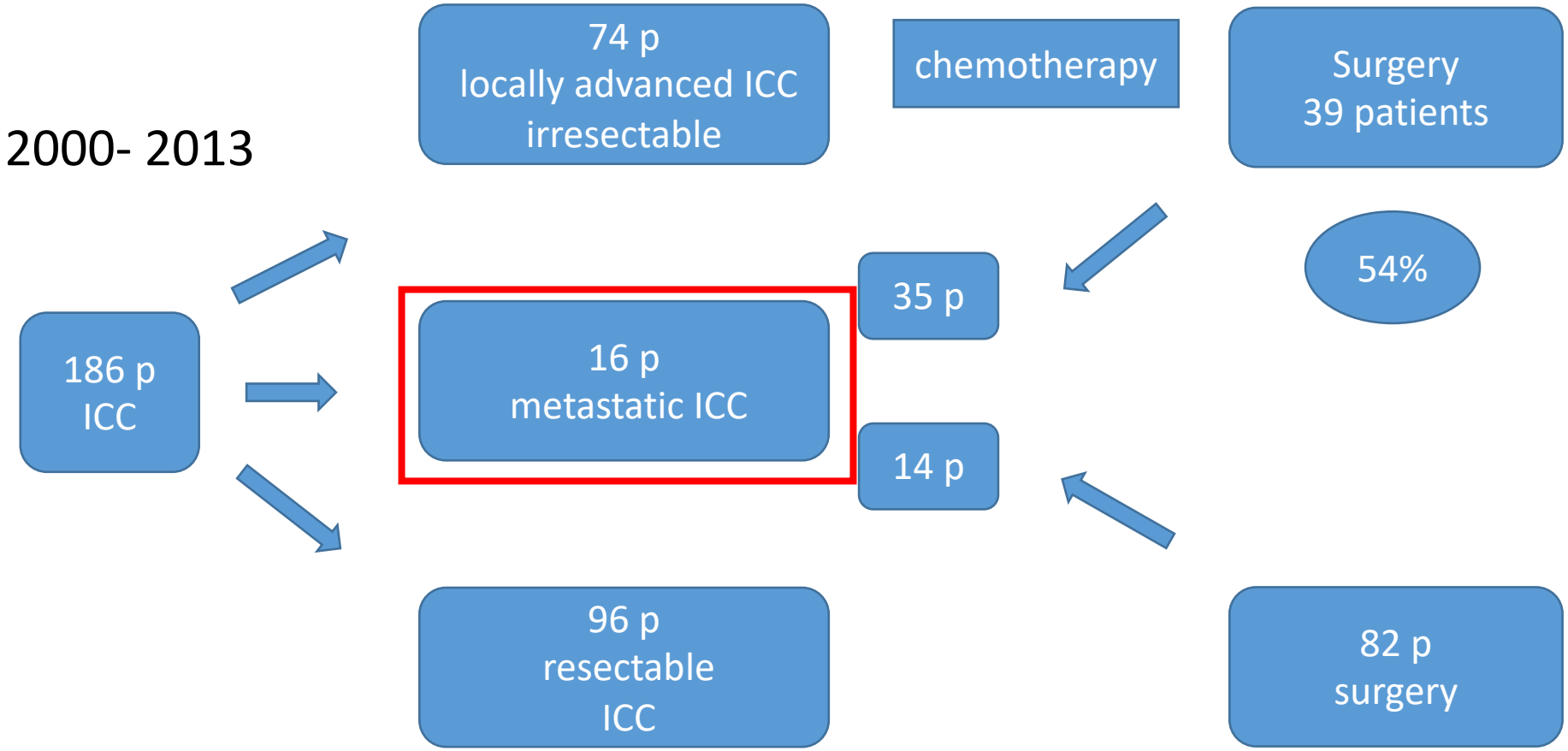


INTRAHEPATIC CHOLANGIOCARCINOMA

Le Roy B, Gelli M, Pittau G, et al. Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. *BJS*. 2018;105(7):839-847. doi:10.1002/bjs.10641

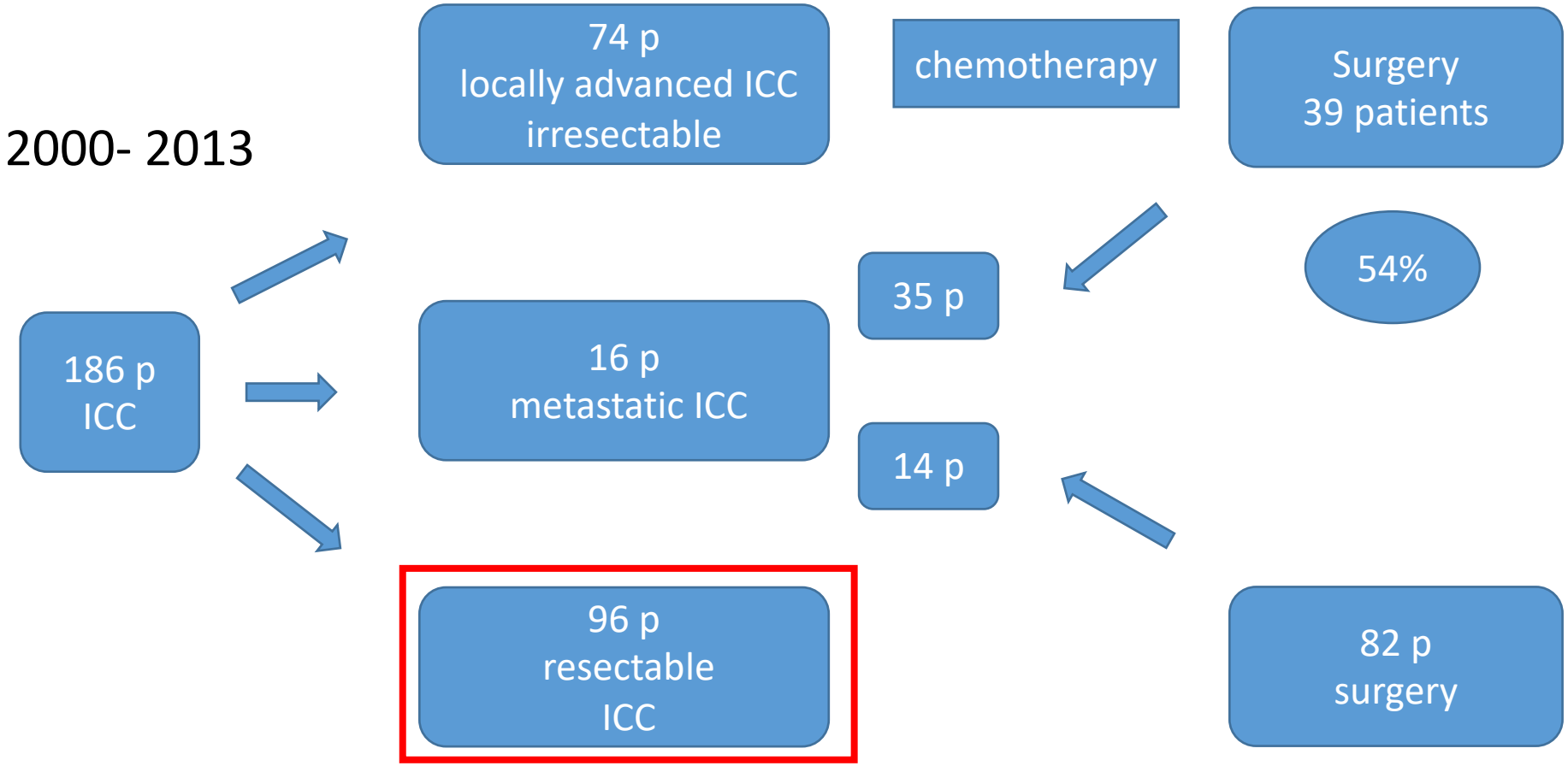


Neoadjuvant treatment : iCCA



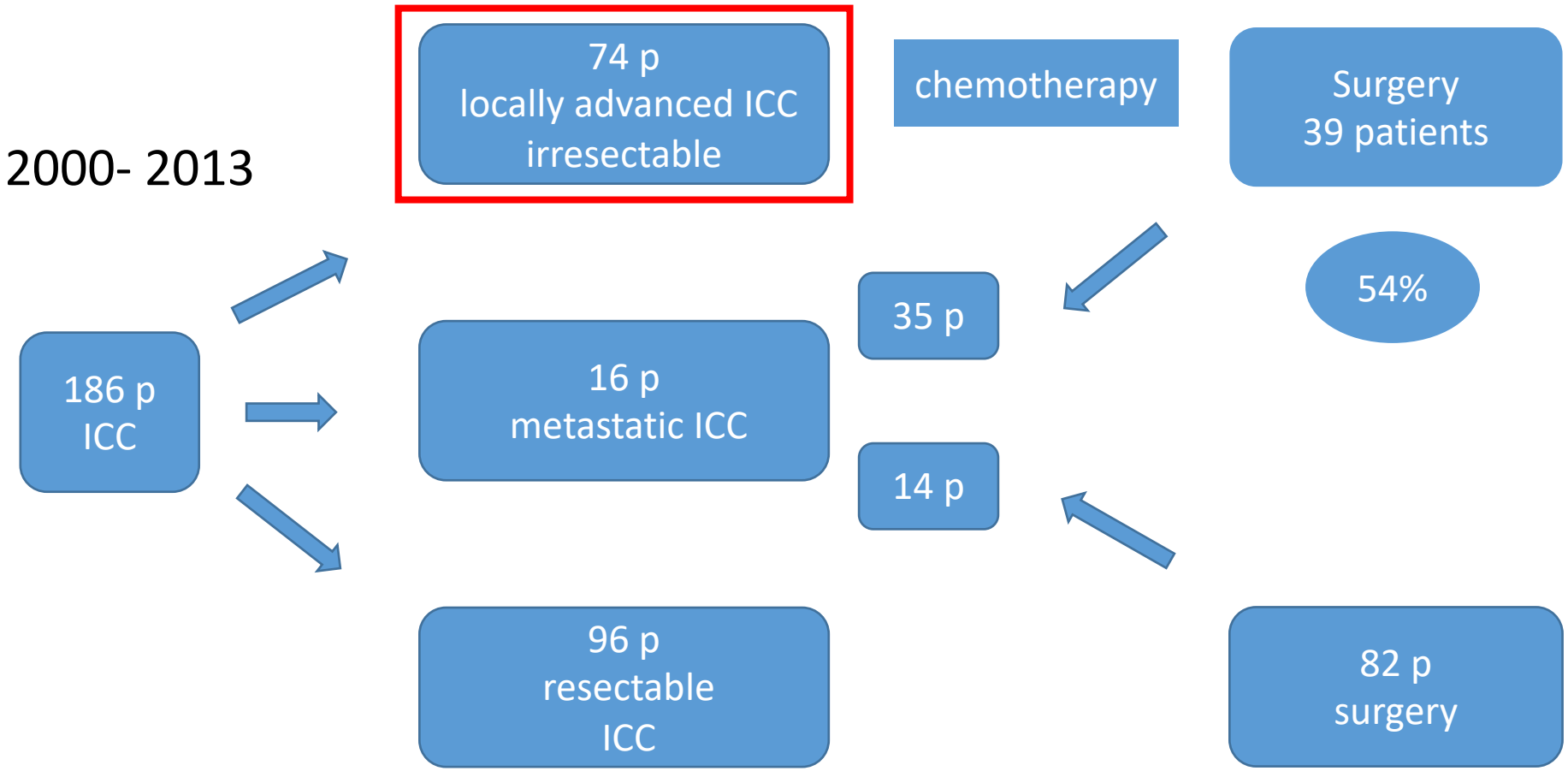
Le Roy; Br J Surg, 2018.

Neoadjuvant treatment : iCCA



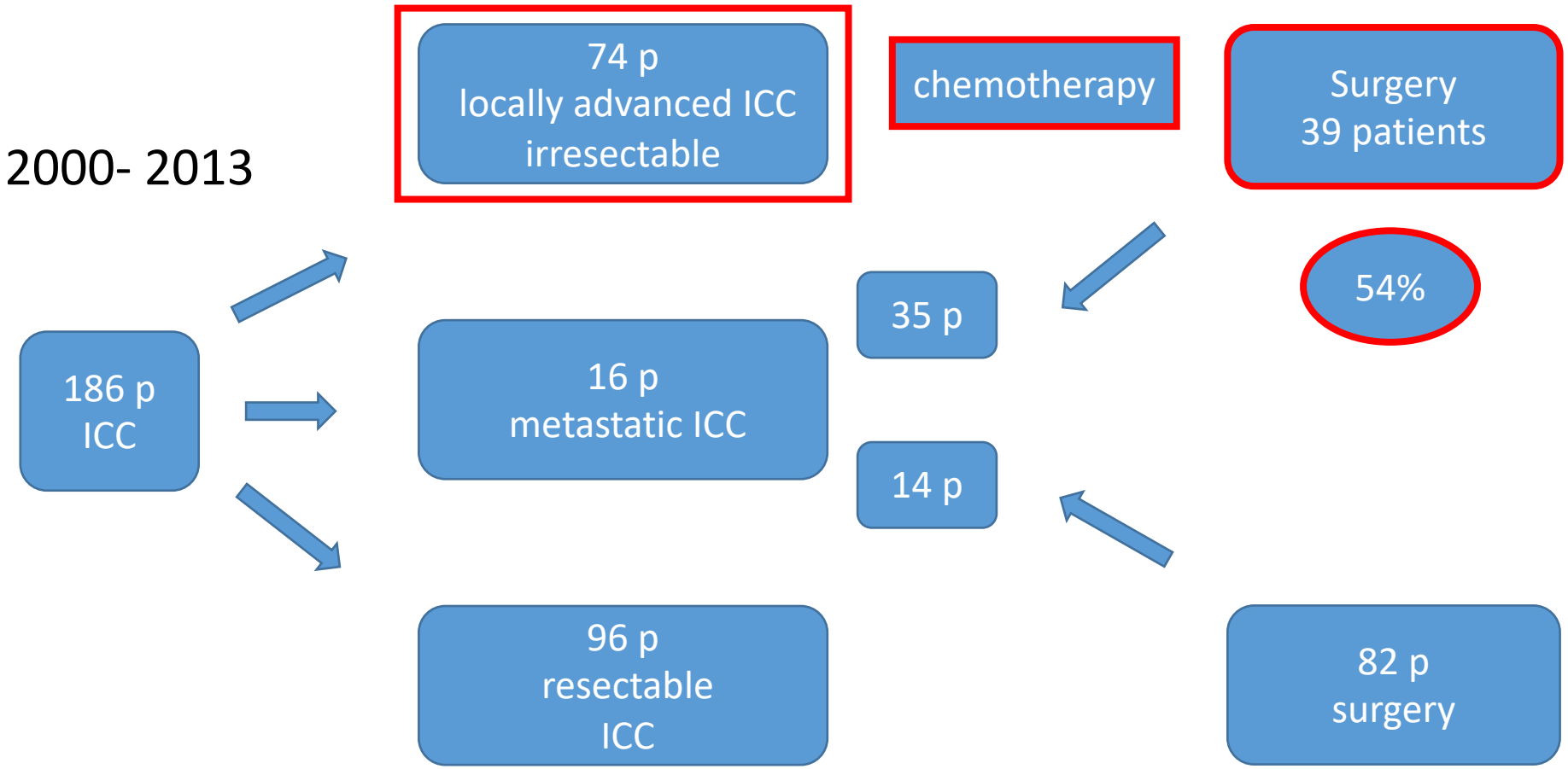
Le Roy; Br J Surg, 2018.

Neoadjuvant treatment : intrahepatic CC



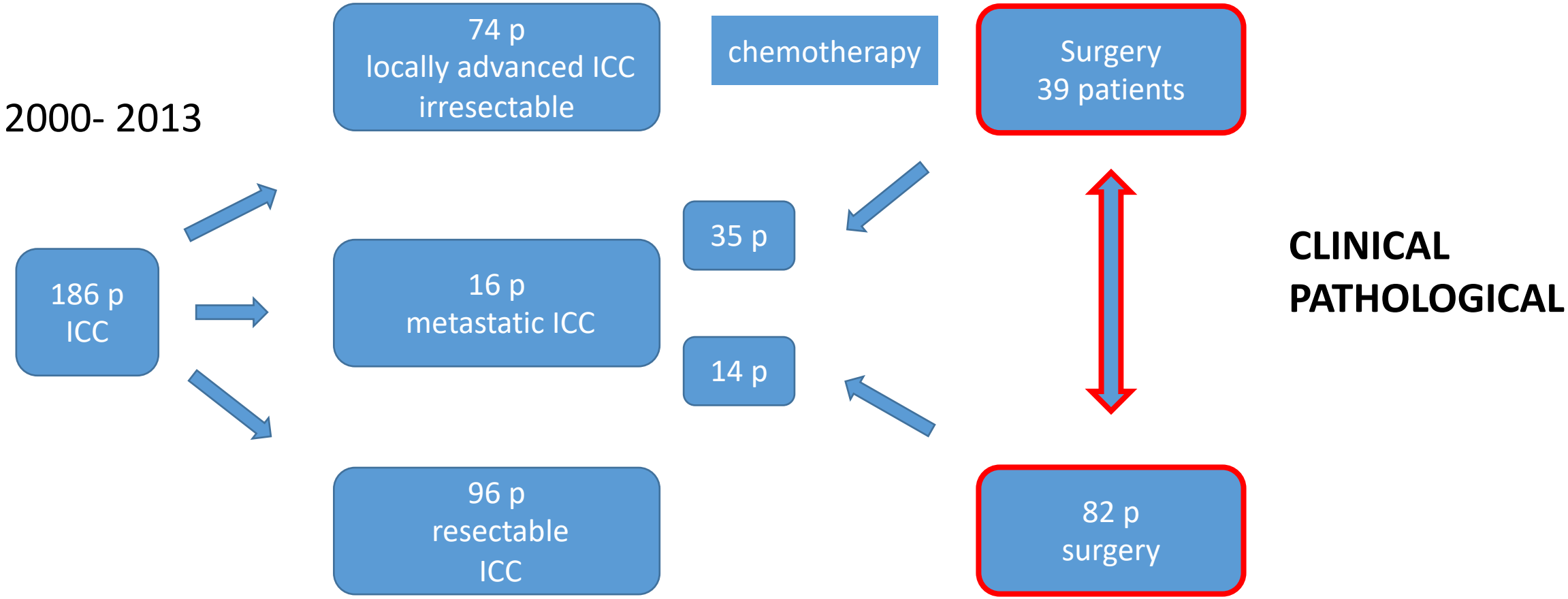
Le Roy; Br J Surg, 2018.

Neoadjuvant treatment : intrahepatic CC



Le Roy; Br J Surg, 2018.

Neoadjuvant treatment : intrahepatic CC



Neo-adjuvant treatment iCCA

Clinical data

Staging at presentation	Surgery after chemotherapy (n=39)	Surgery alone (n=82)	
No. of lesions	2·6(3·3)	1·6(1·8)	0·221
Diameter of largest nodule (mm)	75·0 (57–110)	70·0 (50–93)	0·080
Lymphadenopathy	16 of 38 (42%)	16 of 76 (21)	0·010
Vascular contact or invasion	25 of 35 (71%)	31 of 80 (26%)	
Hepatic metastases	18 (46%)	24 (29%)	0·070

Le Roy; Br J Surg, 2018.

Neo-adjuvant treatment iCCA

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Hepatic metastases	18 (46%)	24 (29%)	0·070

CRITERIA LOCALLY ADVANDED iCCA
contact with the future remaining hepaticorportal veins
contralateral metastases

Le Roy; Br J Surg, 2018.

Neo-adjuvant treatment iCCA

Pathological data

	Surgery after chemotherapy (n=39)	Surgery alone (n=82)	
Positive lymph node	8 (21 %)	15 (18 %)	
Hepatic metastasis	18 (46 %)	30 (37 %)	0·364
Resection			0·004
R0	12 (31 %)	48 (59)	
R1	26 (67 %)	33 (40)	
R2	1 (3 %)	1 (1%)	

Le Roy; Br J Surg, 2018.

Neo-adjuvant treatment iCCA

Pathological data

	Surgery after chemotherapy (n=39)	Surgery alone (n=82)	
Positive lymph node	8 (**21 %**)	15 (**18 %**)	
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Resection			0·004
R0	12 (31 %)	48 (59)	
R1	26 (**67 %**)	33 (**40**)	
R2	1 (3 %)	1 (1%)	

Le Roy; Br J Surg, 2018.

Neo-adjuvant treatment iCCA

Outcome

	CT-surgery	Surgery
mMedian OS	24,1 m	25,7 m
3 yr OS	27 %	21 %
5 yr OS	35 %	24 %

High conversion rate

Comparable outcome

Le Roy; Br J Surg, 2018.

Neoadjuvant treatment : iCCA

Shroff JAMA Onco 2019

Gemcitabine + Cisplatinum + nab Paclitaxel

11 patients unresectable locally advanced CCA I,
9 received surgery after a median of 6 cycles
2 patients achieved a pathologic CR

Rayar M; Ann Surg Onc 2015

The combination of intra-arterial yttrium-90 radioembolization with systemic chemotherapy

8 underwent surgery: R0 resection
10 patients irresectable iHCCA

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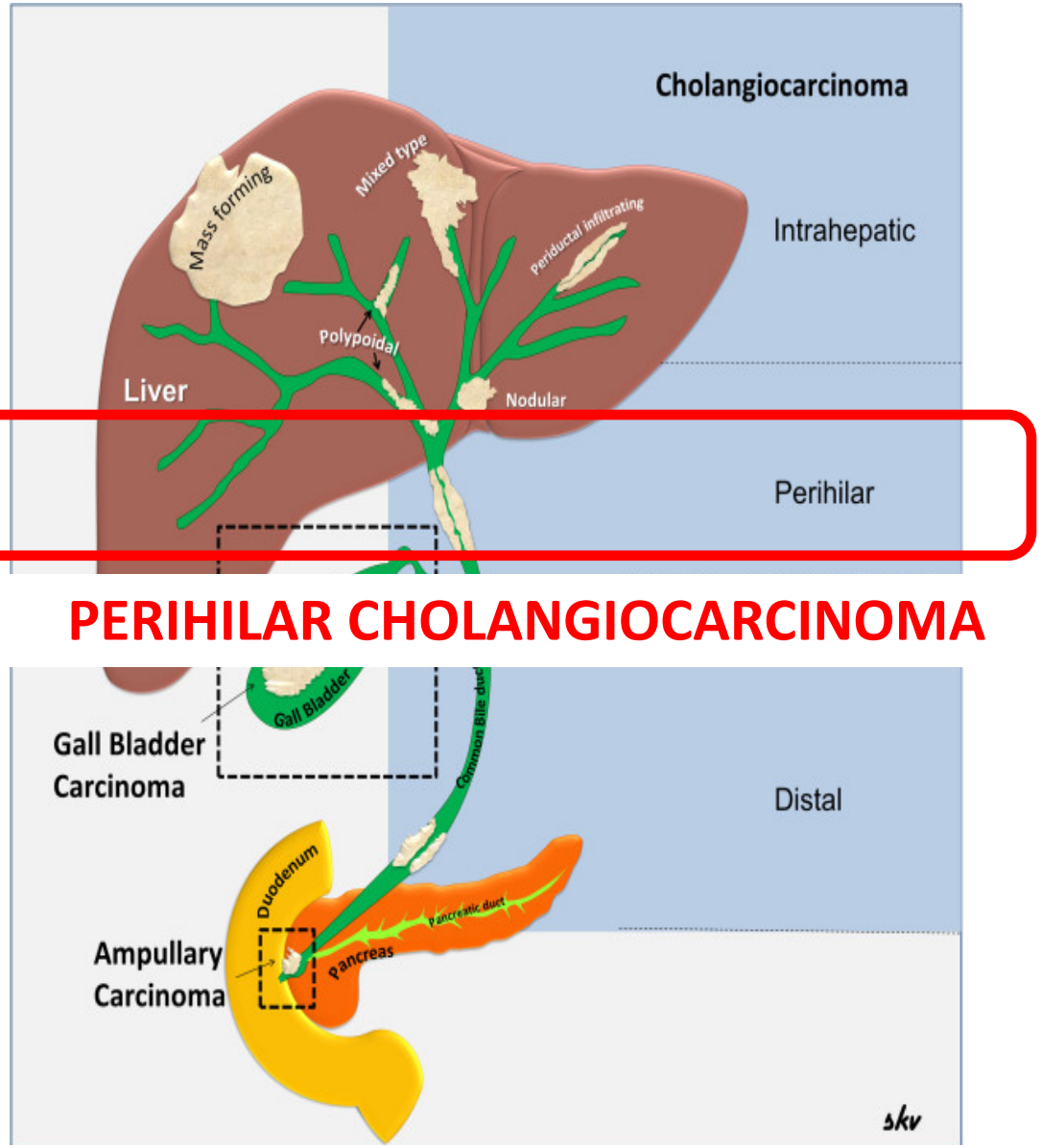


PERIHILAR CHOLANGIOCARCINOMA

MAYO CLINIC PROTOCOL

1993 - 2018

Neoadjuvant Chemoradiation
5-FU with External Beam Radiotherapy (4500Gy)
Brachytherapy with protracted capecitabine

STARTED THERAPY: 349

Staging laparoscopy to exclude metastases or local tumor extension precluding complete resection

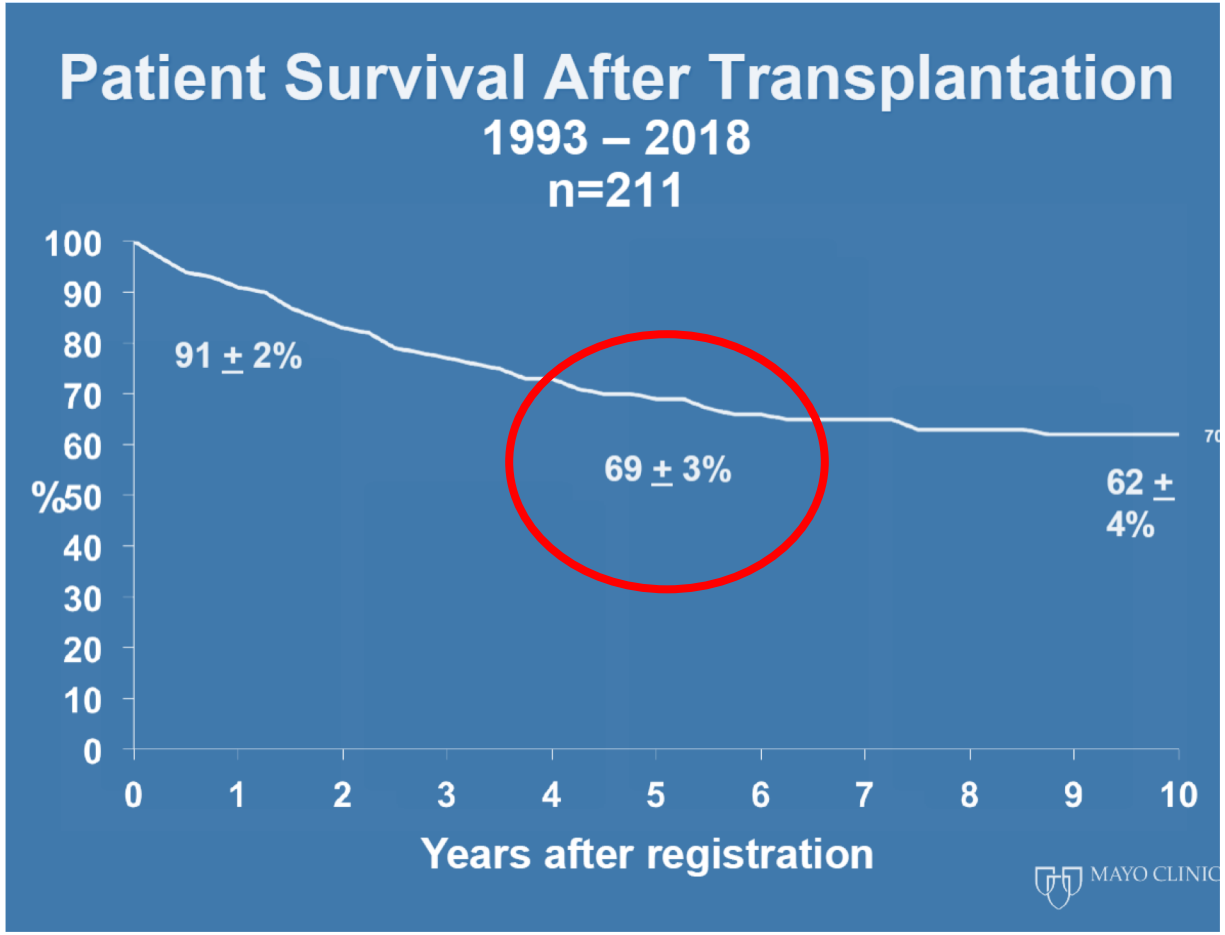
Liver Transplantation

LIVERTRANSPLANTATION: 211

Zamora-Valdes D. Gastroenterol Clin North Am. 2018

MAYO CLINIC PROTOCOL

1993 - 2018



STARTED THERAPY: 349

LIVERTRANSPLANTATION: 211

Neoadjuvant treatment CCA

Neoadjuvant treatment seems feasable and effective but is not standard of care

Neoadjuvant treatment can be offered to the selected patient after MDT discussion

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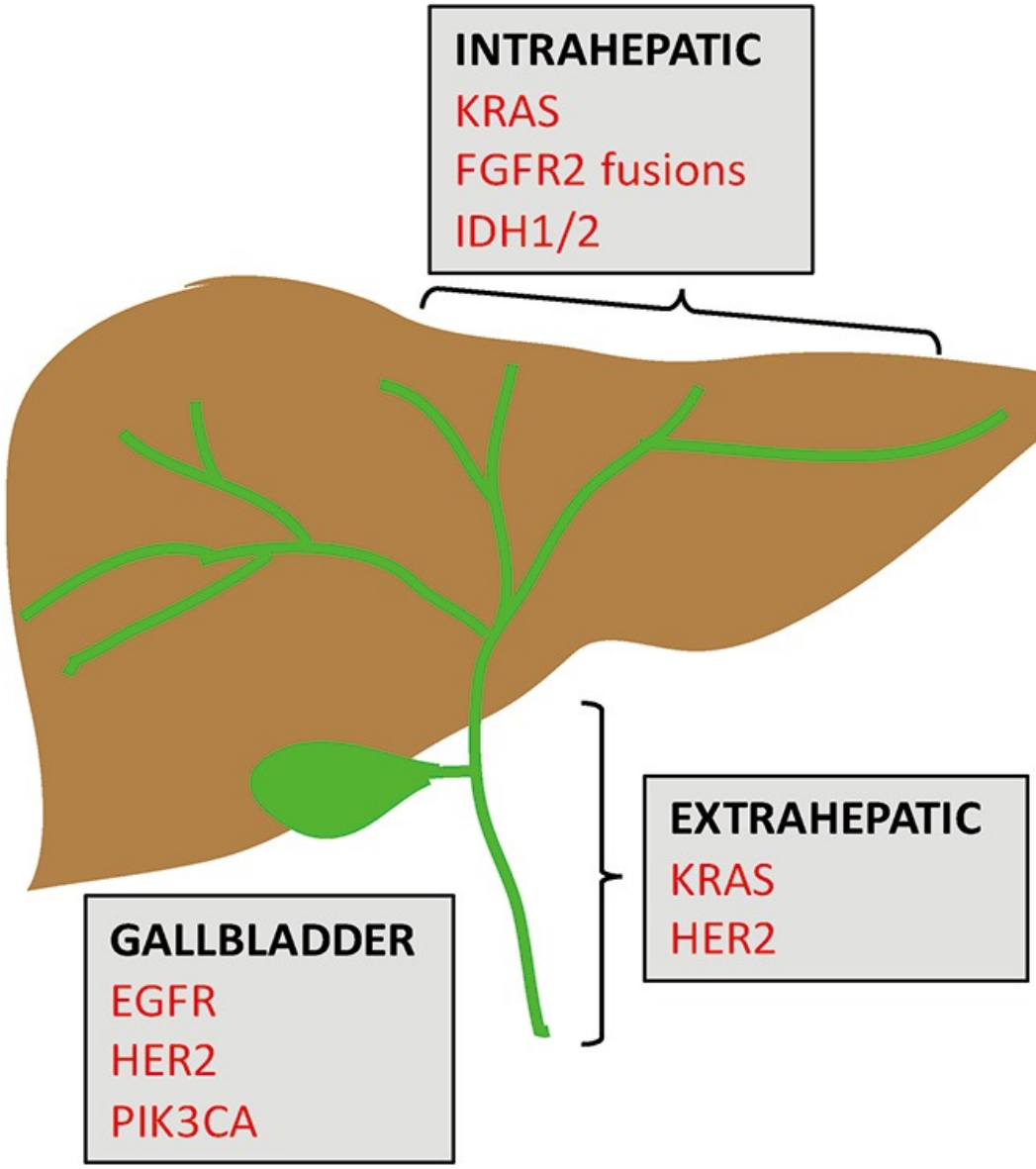
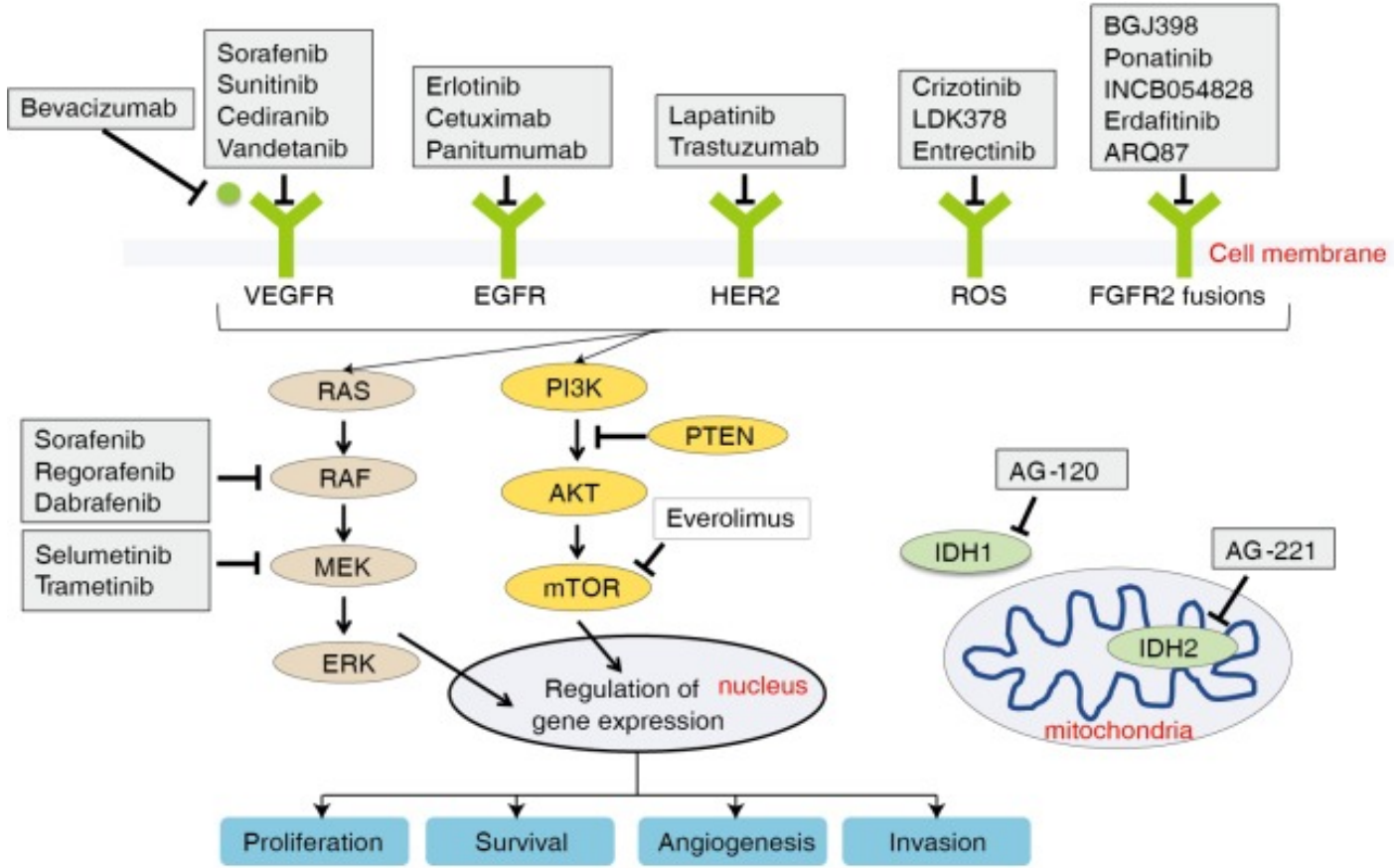
HETEROGENEITY



ONE SIZE DOES NOT FITS ALL

PERSONALISED TREATMENT



ONE SIZE DOES NOT FITS ALL → MOLECULAR PROFILING → INDIVIDUALIZED THERAPY

MULTIDISCILINARY TEAM

+

MOLECULAR BIOLOGIST

GENETICIAN

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Conclusions

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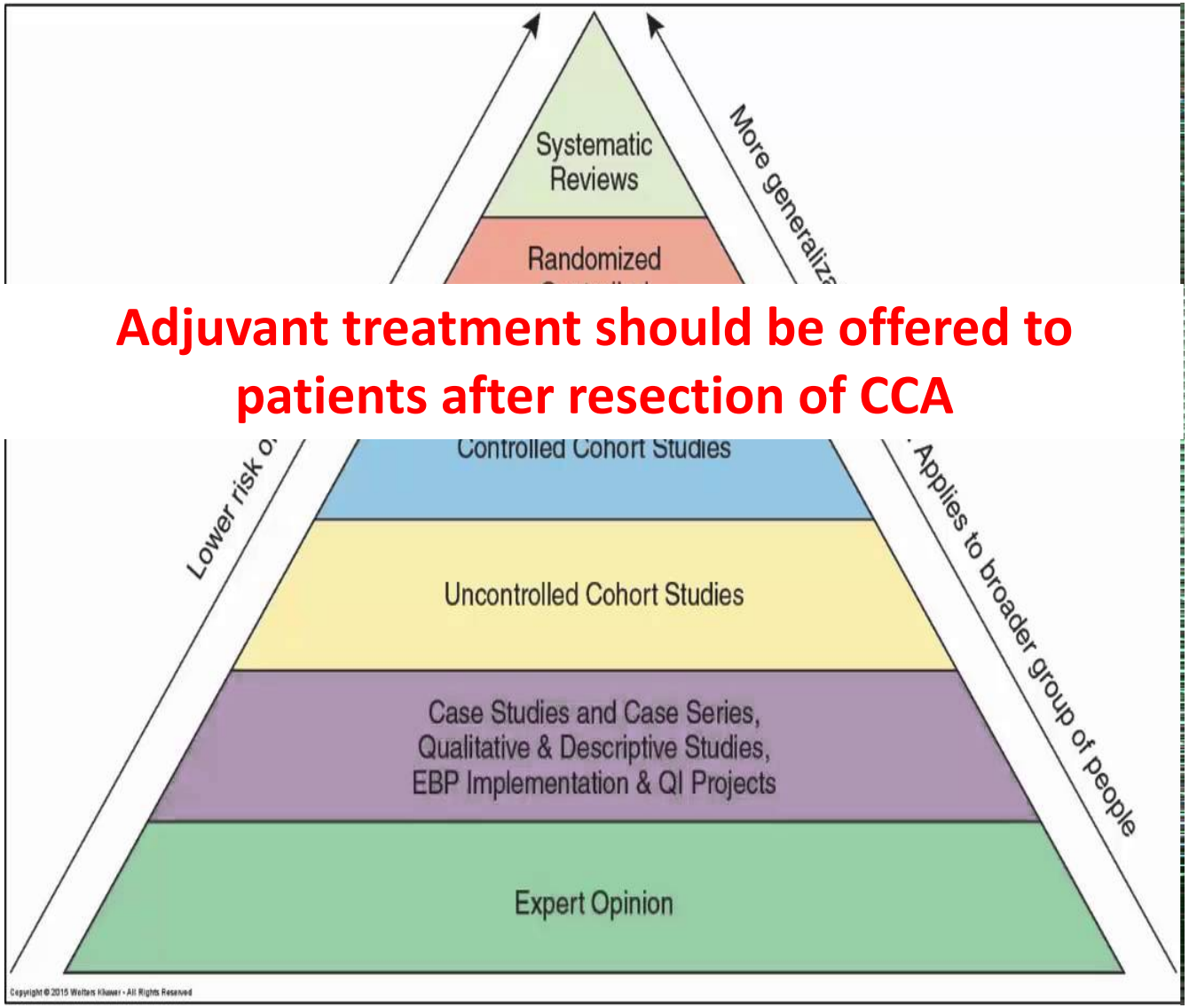

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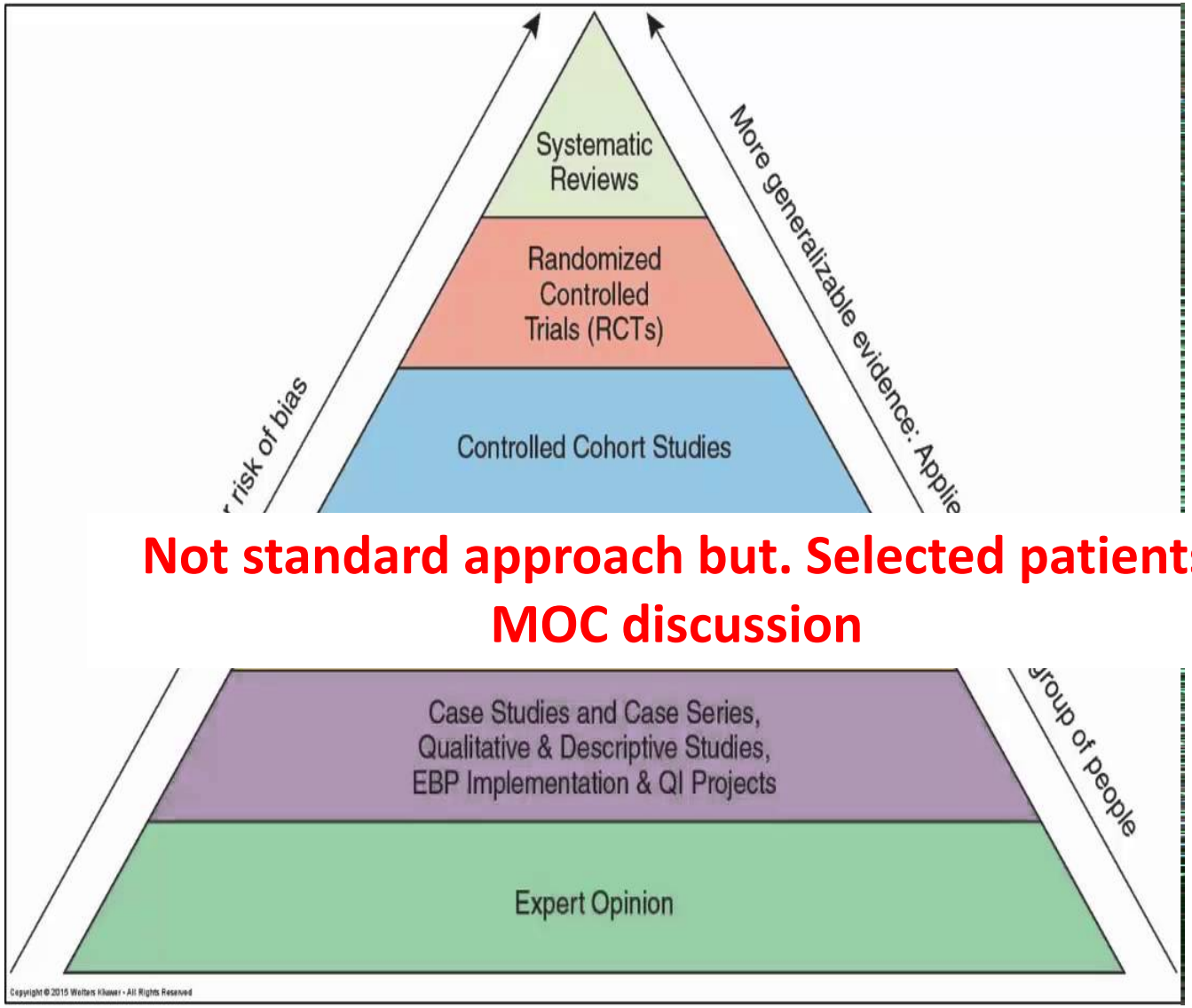

Not standard approach but. Selected patients

MOC discussion

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