



Figure S1. Funnel plots of the performed analyses.

Table S1. Studies excluded after full-text evaluation.

First Author, Year	Study design (centers n)	Study period	Country	Reason for exclusion
Shen, 2004	retrospective single center	1991-2002	USA	CC2 = 52%
Chua, 2011	retrospective multicentric (3)	1988-2009	Germany, Australia, USA	CC2 = 73%
Adachi, 2015	retrospective single center	1992-2012	Japan	CC2 = 70%
Glockzin, 2018	prospective multicenter (10)	2010-2014	Germany	CC2 = 38%
Leimnkuhler, 2019	retrospective and prospective single center	2006-2015	Netherlands	CC2 = 33%
Zhou, 2021	retrospective multicentric (2)	2017-2019	China	CC2 = 40%

Table S2. Newcastle-Ottawa Scale (NOS) for assessing the quality of studies in meta-analyses.

		COHORT STUDY												CASE CONTROL STUDY																			
		S1	S2	S3	S4	C	O1	O2	O3	Total	S	C	O	Quality	S1	S2	S3	S4	C	E1	E2	Total	S	C	E	Quality							
1	Glehen, 2004	1	1	1	1	1	1	1		7	4	1	2	Good																			
2	Elias, 2010	1	1	1	1	1	1	1		7	4	1	2	Good																			
3	Passot, 2012	1	1	1	1	1	1	1		7	4	1	2	Good																			
4	Baratti, 2014	1	1	1	1	1	1	1		7	4	1	2	Good																			
5	Ceelen, 2014	1	1	1	1	1	1	1		7	4	1	2	Good																			
6	Kuijpers, 2014	1	1	1	1		1	1		6	4	0	2	Fair																			
7	Devilee, 2016	1	1	1	1	1	1	1		7	4	1	2	Good																			
8	Maillet, 2016	1	1	1	1	1	1	1		7	4	1	2	Good																			
9	van Eden, 2017	1	1	1	1	1	1	1		7	4	1	2	Good																			
10	Beal, 2020	1	1	1	1	1	1	1		7	4	1	2	Good																			
11	Repullo, 2021			1	1	1	1	1		5	2	1	2	Fair																			
12	Rovers, 2021													1	1	1	1	2	1	1	8	4	2	2	Good								
13	Hanna, 2022	1	1	1	1	1	1	1		7	4	1	2	Good																			
14	Cashin, 2023													1	1	1	1	2	1	1	8	4	2	2	Good								
15	Tonello, 2023													1	1	1	1	2	1	1	8	4	2	2	Good								
Median		7												4	1	2	Good	8												4	2	2	Good

Good: 3-4 S and 1-2 C and 2-3 O/E.

Fair: 2 S and 1-2 C and 2-3 O/E.

Poor: 0-1 S or 0 C or 1 O/E.

Abbreviations. S: Selection; C: Comparability; O: Outcome; E: Exposure.

Table S3. Meta-regression results for severe complications sub-analysis.

	Period	Design	Target therapy	Triplet SC
Baratti, 2014	N	N	N	N
Devilee, 2016	N	N	N	N
van Eden, 2017	N	N	-	N
Beal, 2020	N	N	Y	Y
Repullo, 2021	Y	Y	Y	N
Rovers, 2021	Y	N	Y	N
Cashin, 2023	Y	Y	-	-
Tonello, 2023	Y	Y	Y	Y
Residual heterogeneity (I²)	65.9%	68.3%	65.0%	49.4%
Amount of heterogeneity accounted for (R²)	0%	0%	0%	29.8%
p-value	0.316	0.774	0.251	0.196

Period: studies with median year of patient enrollment after 2009 (year of all included studies).

Design: studies with a design with low-risk of bias (Yes: randomized controlled trials or propensity-score studies) compared to high-risk (No: retrospective series).

Target therapy: studies using target therapy in at least 50% of patients.

Triplet: studies using triplet systemic chemotherapy (FOLFOXIRI).

Y: yes, N: no.