



# Impact of isolated tumor cells in regional lymph nodes in adeno- and squamous cell carcinoma of the esophagus and the esophagogastric junction—A systematic review

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## ABSTRACT

**Background/Introduction:** Isolated tumor cells (ITC) are tumor cells identified in the regional lymph nodes of patients with adeno- or squamous cell carcinoma of the esophagogastric junction (EGJ) or the esophagus. The current staging guidelines for these cancers do not assign any prognostic relevance to ITC, but their role remains debatable. We evaluated current literature to provide an overview of the prognostic relevance of ITC in regional lymph nodes of patients diagnosed with node negative cancer of the esophagus and EGJ.

**Methods:** A systematic search of several databases according to PRISMA guidelines. Three main criteria for inclusion were selected: 1. The studies had to include a group of patients with histopathologically identified ITC as defined by the Union for International Cancer Control Tumor, Node, Metastasis-classification 8<sup>th</sup> edition. 2. The studies had to include a group of patients classified as pN0. 3. The studies had to present the survival rate of patients with pN0, ITC.

**Results:** A total of five studies met the inclusion criteria. Combined, the studies included 434 pN0-patients of which 88 patients had ITC when evaluating the lymph nodes more extensively. The rate of ITC varied from 8% to 56% between studies. Significant differences in surgical techniques, neoadjuvant treatment and histological subtypes were observed. Three studies found a significant prognostic impact of ITC while one did not, and one had conflicting results. The largest difference in 5-year-survival was 33% for patients with ITC compared with 60% without ITC.

**Conclusion:** Although, the results were conflicting, ITC appeared to be a negative prognostic factor in esophageal and EGJ cancer. However, heterogeneity between the studies did not allow for a definitive conclusion.

## 1. Introduction

The incidence of esophageal and esophagogastric junction (EGJ) carcinoma has increased over the past years in the western world and is predicted to increase further due to a rise in alcohol consumption and physical inactivity [1]. Early detection and treatment are essential to improve the prognosis. However, while diagnostic methods and treatment have improved, many patients still suffer from recurrence. Esophageal cancer has an expected 5-year-survival rate (5-Y-S) varying from < 1-30% when lymph node metastases are present [2]. Recurrence is most likely linked to lymph node involvement, as this is the strongest prognostic predictor for EGJ cancer with pN3 (> 6 lymph nodes with metastases) patients having a 5-Y-S of 2–17% compared with up to 83% in patients with pN0 stage (no lymph node metastases) [3].

In order to detect lymph node metastases a lymphadenectomy is performed in combination with resection of the primary tumor. The harvested lymph nodes are subsequently examined histopathologically along with the resected specimen. According to the Union for International Cancer Control Tumor, Node, Metastasis-classification, eight edition (UICC TNM 8<sup>th</sup> edition) guidelines on lymph node involvement in esophageal and EGJ cancer, the presence of tumor cells exceeding 0.2 mm in greatest extent, is categorized as a metastasis. Single cells or clusters of tumor cells less than 0.2 mm in greatest extent should be classified as isolated tumor cells (ITC), pN0(i+) [4]. These small groups of tumor cells can be difficult to identify with certainty by routine Hematoxylin and Eosin (HE)-staining. However, applying immunohistochemical (IHC) staining for cytokeratin highlights the small tumor cell clusters, making them easier to detect. The arbitrary cut off at 0.2 mm has prompted researchers to investigate the impact of these

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small groups of tumor cells, which have had several different names and definitions (micrometastasis, occult lymph node metastasis, minimal tumor involvement etc.) as no common terminology existed. A micrometastasis is defined as a small cluster of tumor cells larger than 0.2 mm, but no larger than 2 mm in greatest extent [4,5]. Micrometastasis is often referenced in the literature; however they are not included in UICC TNM 8<sup>th</sup> edition staging algorithms for esophageal – and EGJ cancer [4].

One hypothesis considers ITC as viable metastases; however they are typically describes as lacking classic metastatic features eg. stromal reaction or proliferative activity [6]. Although the viability and impact of ITC has been debated for the past 20 years, still no consensus has been attained. [5,7]. The UICC TNM 8<sup>th</sup> edition and the AJCC 8<sup>th</sup> edition do not currently ascribe any significance to ITC regarding the node category of esophageal- and EGJ cancer or any other type of cancer except for malignant melanoma of the skin and Merkel cell carcinoma [4,8]. Hence, identified ITC in esophageal- and EGJ cancer have, no impact on treatment. UICC TNM and AJCC have most likely taken their watchful position towards ITC due to the absence of strong evidence for a negative prognostic impact of ITC in most types of cancer including esophageal – and EGJ cancer.

The aim of this review was to evaluate the prognostic relevance of ITC in patients primarily diagnosed with node negative cancer of esophagus and EGJ.

## 2. Methods

### 2.1. Search strategy

Before the search strategy was initiated, the protocol details for the study was submitted to PROSPERO (reg. number: CRD42017076738) [9]. In order to have the highest level of comparability, only studies using the definition of ITC by Hermanek et al. [5] and the current UICC TNM 8<sup>th</sup> edition classification of malignant tumors were included [4]. The size criterion of the ITC definition has remained unchanged since UICC TNM 6<sup>th</sup> edition. In the 7<sup>th</sup> edition an additional criterion has been proposed for breast cancer including clusters of 200 or fewer tumor cells in a single cross-section as ITC. This is not a well-defined criterion for esophageal and EGJ cancer. Thus, since the size criterion has remained unchanged for more than a decade, several studies published before the 8<sup>th</sup> edition of TNM were included. Additionally, only studies with a group of patients whose tumors, after initial histological evaluation were classified as pN0, were included. This was chosen as it was assumed that any increased risk from ITC would be overshadowed by a “true” lymph node metastasis defined by a size of tumor involvement > 0.2 mm. To evaluate the prognostic relevance of ITC, only studies which showed the survival rate of patients with pN0, ITC were included.

The databases PubMed and Embase were searched strategically for terms according to the PRISMA-guidelines [10]. The search was limited to the English language. The search string was based on a combination of the following MeSH terms: Esophageal, neoplasms, lymph nodes, isolated tumor cells and micrometastasis. To manage the screening process the internet-based program Covidence<sup>®</sup> was used. Two separate reviewers read titles and abstracts in order to determine if they were candidates for full text review. The complete search string is available from supplementary material.

### 2.2. Bias evaluation

The bias-evaluation was performed according to the principles of the Newcastle-Ottawa Scale (NOS) for cohort studies- [11]. Two of the authors scored each study separately before deciding on the final score together. The evaluation mainly focused on comparability in relation to T-categories, surgical method and pathological examination.

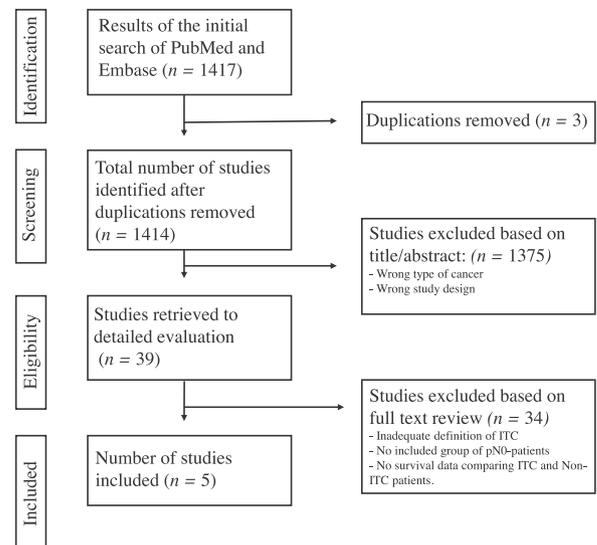


Fig. 1. Overview of the selection process.

## 3. Results

From our search strategy, a total of 1417 studies were identified, of which five studies met the inclusion criteria and were ultimately selected (Fig. 1). The included articles were all retrospective cohort studies including a number of patients ranging from 85 to 146. Two of the studies included patients with tumors having been classified as both pN0 and pN1 (1–3 lymph nodes with metastasis). However, we only included the results of the pN0 group. In the five studies, 88 patients of the total 434, who were primarily classified as pN0, had ITC when evaluating the lymph nodes more extensively with additional levels and supplementary IHC staining [12–16]. This corresponded to a mean ITC incidence rate of 20.3% in the five studies. This evaluation also identified 16 lymph nodes with previously undiscovered metastasis (Table 1).

### 3.1. Definition of isolated tumor cells

An absolute requirement for inclusion in this review was fulfilling the UICC TNM 8<sup>th</sup> edition definition of ITC. In spite of this, slight differences between the studies existed (Table 2).

### 3.2. Histopathological examination

The studies identified ITC by serial sectioning of the lymph nodes that were negative on the initial histopathological examination. In four studies three additional levels were cut and stained with HE and cytokeratin as shown in Table 3. One study differed from this protocol by only adding one level [12]. The thickness of these sections varied between 3 μm and 6 μm. Only two studies registered their distance between levels (250 μm and 300 μm, respectively) [14,16]. Three studies included both squamous cell carcinoma (SCC) and adenocarcinoma (AC) patients [12,14,16], while two studies only included one histological subtype either AC [13] or SCC [15]. In total, the studies included 266 pN0 patients with AC and 168 pN0 patients with SCC.

### 3.3. Percentage of patients with isolated tumor cells and T-category

The incidence rate of ITC varied between the studies. The highest incidence rate of ITC was 56% while the lowest was 8%, with a mean percentage of pN0-patients with ITC of 20.3%. In two studies, the patient population consisted of a high proportion of low T-categories (Tis, T0 and T1) of 44% and 54%, respectively [12,14]. Correspondingly, a

**Table 1**  
Patient characteristics.

Study		MacGuill et al. [12]	Schurr et al. [13]	Thompson et al. [14]	Yekebas et al. [15]	Zingg et al. [16]					
Number of patients		146	85	119	120	86					
Tumor-category	T0/Tis	35	0	28	0	N/A					
	T1	29	22	36	19	N/A					
	T2	19	41	15	27	N/A					
	T3	60	20	40	70	N/A					
	T4	3	2	0	4	N/A					
Node-category	pN0	146	29	119	54	86					
	pN1	0	56	0	66	0					
Histology	AC	95	85	88	0	54					
	SCC	51	0	31	120	32					
NCT (%)		48	14	59	6	34					
Method of surgery*	TTE	N/A	9	119	31	71					
	THE	N/A	20	0	23	15					
Tumor cell micro- involvement	ITC	12	9	22	30	15					
	Metastasis	0	0	9	0	7					
ITC incidence rate (%)		8	31	18	56	17					
ITC incidence rate by histological subtype (%) (AC/SCC)		8.6	2.0	31	N/A	22.7	6.5	N/A	56	28.3	6.3

NCT = Neoadjuvant chemotherapy in a pooled group of pN0 and pN1 patients; TTE = Transthoracic esophagectomy; THE = Transhiatal esophagectomy; ITC Rate = The fraction of patients with ITC to total number of patients; N/A = Not available.

\* Surgical intervention performed on pN0-patients.

low incidence rate of ITC was reported in these studies. Three studies [12,14,16] including both AC and SCC found the ITC incidence rate to be at least three times higher in patients with AC compared with SCC patients.

### 3.4. Surgical techniques

Of the five studies, only one study used the same surgical approach for all the patients. This study performed a transthoracic esophagectomy (TTE) on all patients [14]. The remaining studies either used a combination of different techniques or did not disclose any information regarding the surgical method. Only patients, who underwent radical surgery (R0-resection) were included in all five studies. By adding the numbers of the studies that described their surgical method, it was found that 230 pN0 patients had a TTE performed while 58 had a transhiatal esophagectomy (THE) performed. For the remaining 146 pN0 patients no data regarding the type of surgery was available.

### 3.5. Lymph nodes

The mean number of lymph nodes harvested during the lymphadenectomy varied from 5.5 to 25.9 [12–16]. The extent of the lymphadenectomy was assessed based on the description of the surgery. In two studies the patients had a D1-resection (limited and local lymphadenectomy) performed [14,15] and in the remaining three studies a D2-resection (extended lymphadenectomy) was performed [13,15,16].

**Table 2**  
Definitions of isolated tumor cells.

Study	Criteria for isolated tumor cells	Source
MacGuill et al. [12]	Defined as single tumor cells or clusters of tumor cells < 0.2 mm*	Staging in accordance to the 6th AJCC staging Manual with addition of TNM shorthand notion for isolated tumor cells.
Schurr et al. [13]	Single cells or clusters of cells of less than 0.2 are defined as isolated tumor cells.	Hermanek et al. (1999)
Thompson et al. [14]	Isolated tumor cells were defined as a single tumor cell or cluster of tumor cells < 0.2 mm in size. With the additional criteria: Nuclear enlargement, pleomorphism, hyperchromasia and increased nuclear-cytoplasmic ratio.	Hermanek et al. (1999) Jamieson et al. (2009)
Yekebas et al. [15]	In a histopathologically non-metastatic lymph node isolated tumor cells were defined as the presence of single cells or cell clusters with a positive IHC-staining and a size of not more than 0.2 mm*	Izbicki et al. (1997) Tanabe et al. (2003)
Zingg et al. [16]	Two gastrointestinal pathologists evaluated all slides independently. Those measuring less than 0.2 mm were classified as isolated tumor cells.	Hermanek et al. (1999) Hermanek et al. (1999)

\* Minor paraphrasing has been made to increase clarity.

No studies described a D3-resection (3-field lymphadenectomy).

### 3.6. Oncological treatment

Neoadjuvant chemotherapy (NCT) was a part of the treatment in all studies and was practiced according to different regimens. The percentage of patients who received neoadjuvant treatment ranged from 6% to 59%.

### 3.7. Survival

Three studies found that ITC had a negative prognostic impact on survival [12–14], while one study found no apparent correlation between ITC and survival [16]. In the remaining study by Yekebas et al. [15] conflicting results were found as ITC were reported to have no negative prognostic impact when comparing pN0 patients with and without ITC. However, a 4-fold stratification of surgical method (TTE vs. THE) and ITC status (ITC-positive vs. ITC-negative) for pN0 patients showed a distinct survival benefit for the subgroup of TTE, ITC-negative patients.

The largest survival difference in 5-Y-S related to ITC was 33% for patients with ITC compared with 60% without ITC [14]. The largest difference in median survival was 21 months for patients with ITC and 53 months for patients without ITC [12] (Table 4). In the three studies that included both SCC and AC multivariate analysis was performed [12,14,16]. In two studies this analysis found no significant difference

**Table 3**  
Characteristic of pathological examination.

Study	MacGuill et al. [12]	Schurr et al. [13]	Thompson et al. [14]	Yekebas et al. [15]	Zingg et al. [16]
Nodes					
Harvested	11.6	19.6	5.5	25.9 (TTE) 14.6 (THE)	N/A
Examined	11.6	5.7	5.5	6.8	14
Cytokeratin antibody	MNF-116	Ber-EP4	AE1 /AE3	BER-EP4	LU-5
Sections	1	6	6	6	6
Levels	1	3	3	3	3
Thickness (µm)	4	4-6.	4	4-6.	3
Distance (µm)	N/A	N/A	250	N/A	300
D-resection level	D1	D2	D1	D2	D2

TTE = Transthoracic esophagectomy; THE = Transhiatal esophagectomy; Nodes = Mean number of Lymph nodes; Distance = number of µm between sections; N/A = Not available.

in overall survival between SCC and AC [14,16]; however one study found significantly better prognosis for AC compared with SCC [12]. Furthermore, one study made a comparison of the prognostic impact of IHC-positive cells (either ITC or MM positive cells) stratified by histological subtype [16]. This study found a significantly better disease-free ( $p < 0.02$ ) and overall survival ( $p < 0.01$ ) in IHC negative patients with SCC. For the AC group no, significant difference was seen. The two other studies did not allow for a comparison of the prognostic impact of ITC stratified by histological subtype.

### 3.8. Bias evaluation

Bias-evaluation was performed according to NOS-guidelines [11]. The categories assessed were selection criteria, comparability and outcome. In general, a low level of bias was observed with scores ranging from 6 to 7 with the highest possible score being 10. The primary difference in the bias score was found in the comparability category (Table 5). In this category three studies attained a score of 1 [12,13,15] and two studies attained a score of 2 [14,16] with the highest possible score being 4.

## 4. Discussion

The results of this review points towards a negative prognostic impact of ITC, as the majority of the studies found a correlation between ITC and reduced survival in SCC and AC of the esophagus and the EGJ. The majority of the studies in this review, however, only reported a negative prognostic impact of occult lymph node metastases and not an increased risk of relapse [13–16]. To our knowledge, this is the first systematic review to only include studies that strictly adhered to the definition of ITC according to UICC TNM 8<sup>th</sup> edition.

Interestingly, the strongest prognostic impact of ITC was identified in the two studies that included the most pN0-patients [12,14]. These two studies alone accounted for 61% of the included pN0 patients. In one study finding no apparent prognostic impact of ITC on survival, a 4-fold stratification of the surgical method (TTE vs. THE) and ITC status for pN0 patients was reported to show a distinct survival benefit for TTE, ITC-negative patients [15]. Together with the findings that significantly more lymph nodes were harvested with TTE compared with THE (mean 25.9 vs. 14.6, respectively,  $P < 0.001$ ) [15], the results

indicate a negative prognostic impact of ITC, despite the risk of bias from stage migration, the small number of patients and the short follow-up-period.

Although most of the studies included in this review point towards a negative prognostic impact of ITC in esophageal and EGJ cancer, the heterogeneity between the studies presents a great challenge when comparing their results. This might also be the reason for the somewhat conflicting results in earlier reviews and this is reflected in the bias evaluation where the lowest scores were observed in the comparability category. One source of heterogeneity between the studies was the surgical procedure where both the TTE and THE-procedures were performed. The THE-procedure has been argued to be disadvantageous compared with TTE because it leads to fewer lymph nodes resected [17]. This could potentially lead to stage migration as missed lymph nodes with ITC or metastases would negatively impact the survival in patients believed to be pN0, ITC negative. The consequence of this would be a reduced difference in survival when comparing ITC negative with ITC positive patients. This is in line with the findings of Yekebas et al [15]. Another limitation was the extent of the lymphadenectomy, which was limited to either a D1- or D2 field. According to the UICC TNM 8<sup>th</sup> edition, a minimum of seven lymph nodes is required and AJCC 8<sup>th</sup> edition requires a minimum of ten lymph nodes depending on the T-category [4,8]. While four of five studies fulfilled these minimum resecting requirements, two of the studies did not histologically examine all the resected lymph nodes [13,15]. Hence, only two studies examined more than seven lymph nodes. This inadequate lymph node examination may have resulted in fewer identified ITC. However, no apparent connection between the ITC incidence rate and the mean number of examined lymph nodes was found.

Another source of heterogeneity is differences in the pathological examination. Only one of the five studies had two independent pathologists reviewing the lymph nodes. No consensus on the distance between the levels examined existed. In two studies, the distance exceeded 200 µm making it possible to miss ITC or even a metastasis [14,16], and three studies did not mention the distance [12,13,15]. Also, the maximum number of levels was three, which might be insufficient to completely rule out the presence of ITC. Another source of heterogeneity was the different T-stages. Studies with a majority of low T-category patients tended to have a lower rate of ITC. The wide range of T-categories also makes comparison of lymph node involvement and

**Table 4**  
Survival in patients with ITC compared with patients without ITC.

Study	Number of patients (pN0)	Survival (ITC vs. Non-ITC)	P-value
MacGuill et al. [12]	146	21 vs. 53 months median survival	$P < 0.05$
Schurr et al. [13]	29	65 months vs. median survival not reached*	$P = 0.05$
Thompson et al. [14]	119	33 vs. 60 % 5-Y-S	$P = 0.014$
Yekebas et al. [15]	54	96 vs. 113 months median survival	$P = 0.158$
Zingg et al. [16]	86	62.6 vs. 57.7 % 5-Y-S	$P = 0.708$

\* To few people had died to calculate the median survival; 5-Y-S = 5 year survival.

**Table 5**  
Newcastle-Ottawa Scale bias evaluation.

Study	MacGuill et al. [12]	Schurr et al. [13]	Thompson et al. [14]	Yekebas, et al. [15]	Zingg et al. [16]	
Selection	Was the cohort truly representative? <sup>*</sup>	no	yes	no	yes	no
	Was the patients without ITC drawn from the same cohort as those with ITC?	yes	yes	yes	yes	yes
	Did the study attain exposure through surgical records?	yes	yes	yes	yes	yes
	Was no interest of outcome present at the start of the study?	yes	yes	yes	yes	yes
Comparability	Did the study only included either ACC or SCC patients?	no	yes	no	yes	no
	Did the study only include patients from pN0-stage?	yes	no	yes	no	yes
	Did more than one pathologist review the LN's?	no	no	no	no	yes
	Did the study use only more than one surgical technique?	no	no	yes	no	no
Outcome	Did the study have a 5 year follow up period?	yes	yes	yes	yes	yes
	Did the study account for loss of follow up?	yes	yes	yes	yes	yes
Total number of points	6	7	7	7	7	

\* A truly representative cohort was defined as a cohort without a majority of patients with low T-category.

5-Y-S difficult, as the latter is strongly affected by the T-category [8]. Finally, a major concern is that three studies included both AC and SCC. AC and SCC are different entities that cannot be directly compared. Unfortunately, only few of the previous studies discriminated among these different tumor types and separate reviews were not possible. This might affect the incidence rate of ITC since ITC were reported far more often in AC than in SCC in the studies that included both types [12,14,16]. Furthermore, overall survival is generally thought to be slightly better for AC compared to SCC [18,19]

Combined the heterogeneity of the pathological examination, the surgical method, histological subtypes and the T-stages might explain some of the variance in the incidence rate of ITC observed in this study.

The results of this review are in line with the findings of a prior review, which also reported survival and ITC incidence rate in esophageal and EGJ cancer [20]. This meta-analysis found that patients with occult lymph node metastases (OLNM) had a hazard ratio of 3.16 (95% CI 2.25–4.42) for disease relapse compared with node negative patients [20]. However, another systematic review focusing on prognosis had conflicting results with only seven of 13 included studies reporting a negative prognostic impact of lymph node micrometastasis (LNM) [21]. It should be noted that both reviews included studies that used widely unspecific terms (LNM and OLNLM) without a clear definition to categorize tumor cells in lymph nodes. These definitions included any tumor cells or clusters of tumor cells identified by IHC in a patient staged as pN0 by HE-staining and no differentiation between ITC and MM was made [20,21].

Recent large-scale studies of malignant melanomas of the skin and breast cancer have also provided evidence of a negative prognostic impact of ITC [22–25]. A review of breast cancer concluded that detection of ITC in lymph nodes by sentinel node examination has a hazard ratio of 1.5 (95%CI 1.15–1.94) for a disease event, if the patients did not receive adjuvant chemotherapy [25]. Another cohort study with more than 3000 breast cancer patients concluded, that patients with ITC had a significantly reduced 5-year-disease free survival [22]. Similarly, a study found that ITC in sentinel nodes correlated to a reduced disease-free survival (74 vs. 89 months) in malignant melanoma [24]. The results of above-mentioned studies indicate that ITC have a significant negative prognostic impact at least in some types of cancer [22–25]. However, comparable large-scale studies have not been performed for esophageal and EGJ cancer.

In conclusion, this systematic review found that ITC appeared to be a negative prognostic factor in esophageal and EGJ cancer. However, heterogeneity between the studies did not allow for a conclusive recommendation of the importance of ITC. Further research concerning ITC is required to determine their role. It is very important that future studies discriminate between AC and SCC. These studies should follow the ITC definitions used by UICC TNM and AJCC, include a

representative patient population and finally serial sectioning of lymph nodes with additional staining should be performed.

#### Conflict of interest

The authors declare they have no conflict of interest.

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