THE PROGNOSTIC VALUE OF LYMPHATIC METASTASIS ON FIVE-YEAR SURVIVAL IN CERVICAL CANCER

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ABSTRACT:

BACKGROUND: It is generally known that the occurrence of metastases, in most types of cancer, reduces the overall survival. However, current detection methods for lymphatic metastasis are highly invasive and the accuracy is limited. Furthermore, treatment is very invasive. That is why it is essential to gain knowledge about the influence of lymphatic metastasis in patients with cervical cancer on their five-year survival.
OBJECTIVE: To study the effects of lymphatic metastasis in patients with cervical cancer on their five-year survival.
METHODS: A Pubmed and Embase library search was performed to find applicable articles. After exclusion of non-relevant articles and critical appraisal, fourteen articles were selected.
RESULTS: Among patients with cervical cancer, the five-year survival was 1.51 (95% CI 1.38;1.65) times as high in patients without lymphatic metastasis in comparison to patients with lymphatic metastasis. When comparing uni- and bilateral lymph node metastasis, in patients with unilateral metastasis the five-year survival was 1.32 (95% CI 0.92;1.88) times as high as in patients with bilateral metastasis. When analysing the prognostic significance of the number of lymph nodes involved, in patients with only one lymph node involved the five-year survival was 1.54 (95% CI 1.27;1.85) times as high as in patients with more than one lymph node involved.
CONCLUSION: The five-year survival rate in patients with cervical cancer and lymphatic metastasis is significantly worse in comparison to patients without lymphatic metastasis. Prognosis gets worse if more lymph nodes are affected. Whether metastasis occurred unilaterally or bilaterally did not have a significant effect on prognosis.

WHAT'S KNOWN: In most types of cancer metastasis can occur which reduces the overall life expectancy.

WHAT'S NEW: Cervical cancer patients without lymphatic metastasis have a five year survival rate that is 1.51 times as high as in patients with lymphatic metastasis. The five year survival is 90.6% and 60.2%, respectively. When comparing the involvement of only one lymph node and multiple lymph nodes, the five year survival is 1.54 times as high when there is only one lymph node involved.

KEYWORDS: Cervical cancer, Lymphatic metastasis, Five-year survival rate

Introduction

Cervical cancer or cervical carcinoma is a type of cancer caused by abnormal growth of squamous and/or columnar epithelial cells in the cervix. In 2012, an estimated 528,000 women were diagnosed with cervical cancer worldwide, with approximately 24,400 deaths [1]. This makes cervical cancer the 4th most common cause of cancer related deaths in females. Even though most of these deaths occur in less developed regions, where the use of screening programs is not implemented as well as in developed countries, cervical cancer can be described as an important health issue. Metastasis can occur with a prevalence of 0-20% in early stages and a prevalence of 20-92% in late stages of cervical cancer [2]. In the case of lymph-node metastasis, pelvic lymph nodes are usually first affected. However, metastasis can also occur in more cranial or caudal parts of the lymphatic system.

At the moment, there is an ongoing worldwide discussion about the detection of lymph node metastasis. Lymphatic metastasis are currently diagnosed by either using PET/CT scan or lymph node dissection. Lymph node dissection is a very invasive but highly accurate diagnostic technique. PET/CT scan is a less invasive technique, but the accuracy is limited, with a sensitivity of 75% and a specificity of 96% [3]. Treatment of cervical cancer is a very invasive procedure. Patients are treated with chemotherapy, radiation therapy and/or dissection of the affected tissue. Prognosis after treatment is likely to be influenced to great extent by FIGO-stage, lymph node status and tumour volume.

To gain understanding in the importance of the most effective approach of detection and treatment of lymphatic metastasis, we have to gain knowledge about the influence of lymphatic metastasis in patients with cervical cancer on their five-year survival.

Methods

Search strategy and selection

We searched Pubmed and Embase to find studies on the effect of lymphatic metastasis on the five-year survival in patients with cervical cancer. Our search provided us with 4,617 articles in Pubmed and 2,075 articles in Embase. We chose to use an English language filter, because in our time frame no professional translations of other languages could be made. After removing duplicates, there were 4,659 articles left, which were then screened on title and abstract. We used the following inclusion criteria: patients with cervical cancer, lymphatic or lymph node metastasis and five-year survival rate.

We excluded systematic reviews and meta-analysis, and studies that did not perform a survival analysis, did not correct for other prognostic factors, did not have a full text available, or used a lymph node ratio to measure the size of metastases. 36 articles were found to match these criteria. We retrieved the full text of these articles and analysed if they truly matched our inclusion and exclusion criteria; 22 articles were excluded and 14 articles were included.

Critical appraisal

We used the Newcastle-Ottowa Scale critical appraisal-tool to judge the

Table 1: *Critical appraisal according to Newcastle-Ottowa Scale.*

		Criterion scores‡		
Study	**Study design**	**Selection**	**Comparability**	**Outcome**
Alcock et al., 1987 [4]	Cohort	****	*	***
Atahan et al., 2007 [5]	Cohort	***	**	**
Girardi et al., 1993 [6]	Cohort	****	**	***
Hellebrekers et al., 1999 [7]	Cohort	****	**	***
Ho et al., 2004 [8]	Cohort	***	**	**
Hopkins et al., 1993 [9]	Cohort	****	*	***
Hosaka et al., 2011 [10]	Cohort	****	**	**
Inoue et al., 1990 [11]	Cohort	****	*	***
Ishikawa et al., 1999 [12]	Cohort	****	**	**
Liu et al., 2015 [13]	Cohort	***	**	*
Macdonald et al., 2009 [14]	Cohort	***	**	***
Metindir et al., 2009 [15]	Cohort	****	**	***
Nakanishi et al., 2000 [16]	Cohort	****	**	**
Tanaka et al., 1984 [17]	Cohort	****	*	**

‡Star (*) indicates the score given to study according to the Newcastle-Ottowa Scale (NOS) quality assessment scale, with more stars reflecting better quality.

relevance and validity of the selected articles. The articles were ranked by their level of validity, with more stars reflecting better quality (Table 1). Critical appraisal was performed by either two or three authors.

Statistical analysis

Review Manager (RevMan) was used to visualise our results. We chose to use a Random Effects analysis model, because we assumed that the true effect size may vary between our included studies. As a measure of association, we used a Risk Ratio, which represents the increase of survival in the group of patients without lymph node metastasis in comparison to the group of patients with lymph node metastasis. A dichotomous outcome measure was chosen to represent our data, because our outcome measure can only take on two values; "deceased" or "alive".

Subgroup analyses

To analyse the effect of the distribution of lymphatic metastasis, either bilateral or unilateral, and the number of affected lymph nodes on the prognosis of cervical cancer, we collected data from each article containing information about these prognostic factors. When extracting data from the studies discussing the influence of the number of lymph nodes involved, we chose to differentiate between either one or more than one metastasised lymph node. Once again, RevMan was used to visualise the results, using a Random Effects model, Risk Ratio and dichotomous outcome.

Results

Critical appraisal

After validating our articles according to the Newcastle-Ottowa Scale, we found that the fourteen included studies met most of our validity criteria (Table 1). For that reason we chose to include all fourteen studies.

Lymphatic metastasis versus no lymphatic metastasis

All fourteen remaining studies reported the influence of lymph node metastases on the five-year survival of patients with cervical cancer. In all patients with lymphatic metastases the metastases were treated. All studies showed a higher five-year survival rate in patients without lymphatic metastases (Table 2) compared to patients with lymphatic metastasis. All Risk Ratios were higher in the group without lymphatic metastasis. Only one study, Metindir et al. [15], showed a 95% Confidence Interval that contained the value 1; [0.86, 1.34]. We found a pooled Risk Ratio of 1.51 with a 95% Confidence Interval ranging from 1.38 to 1.65. A visual representation of these results can be found in the form of a Forest Plot (Figure 1).

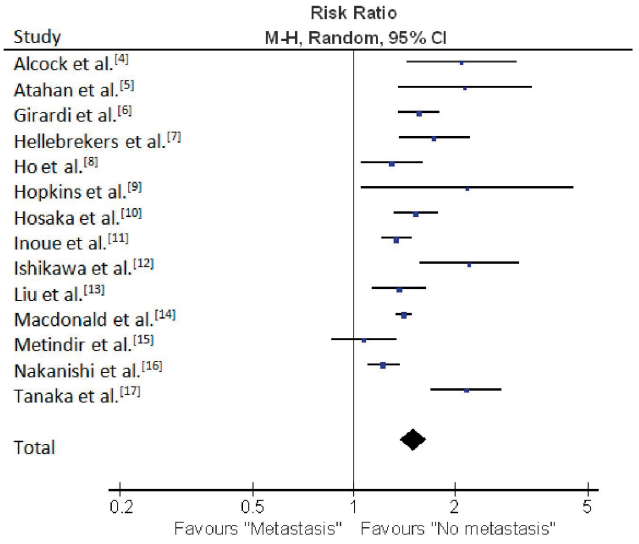

Figure 1: *Forrest plot representing Risk Ratio and Confidence Interval for 5-year survival rate in patients with metastasis compared to patients without metastasis.*

Unilateral lymph node metastasis versus Bilateral lymph node metastasis

Two studies reported the prognostic factors uni- and bilateral metastasis (Table 3). The overall Risk Ratio representing the effect of unilateral metastasis on the survival rate compared to the effect of bilateral metastasis was 1.32, with a 95% Confidence Interval ranging from 0.92 to 1.88. A visual representation of the results can be found in the form of a Forest Plot (Figure 2).

One lymph node involved versus more than one lymph node involved

Seven studies reported the prognostic significance of the number of lymph nodes involved (Table 4). The overall Risk Ratio in these studies was 1.54, with a 95% Confidence Interval ranging from 1.27 to 1.85. A

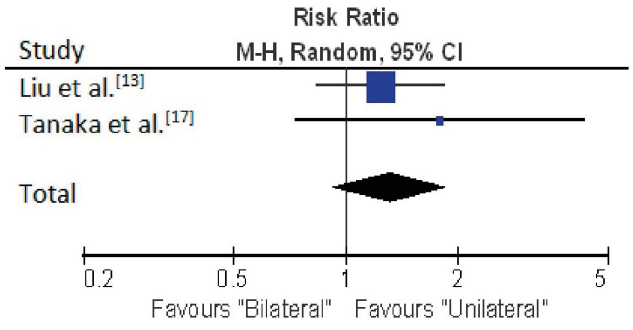

Figure 2: *Forrest plot representing Risk Ratio and confidence interval for 5-year survival rate in patients with bilateral lymph node metastasis compared to patients with unilateral lymph node metastasis.*

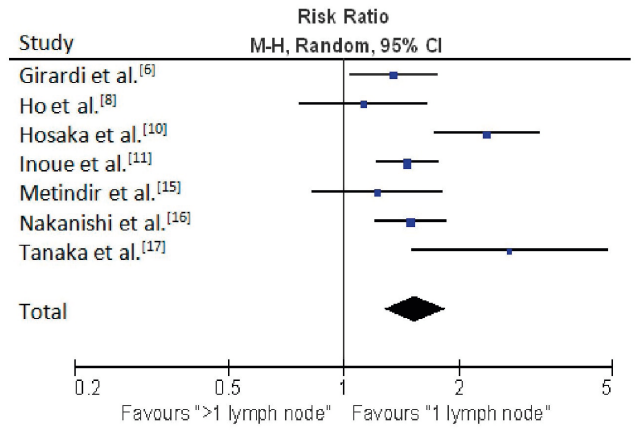

Figure 3: *Forrest plot representing Risk Ratio and confidence interval for 5-year survival rate in patients with multiple lymph node metastasis compared to patients with one lymph node metastasis.*

visual representation of these results can be found in the form of a Forest Plot (Figure 3). The Risk Ratios of five of the studies are mostly homogenous, ranging from 1.13 to 1.49. However, two of the studies, Hosaka et al. [10] and Tanaka et al. [17], showed an aberrant Risk Ratio of 2.35 and 2.70 respectively. Two studies, Ho et al. [8] and Metindir et al. [15], showed a 95% Confidence Interval that contained the value 1.

Discussion

Our results show that, when comparing patients with lymphatic metastasis to patients without lymphatic metastasis, the latter had a significantly higher five-year survival rate (RR of 1.51 and 95%CI 1.38;1.65). This implies that the absence of lymphatic metastasis provides a better prognosis for patients with cervical cancer. In one study, Inoue et al. [11], patients with unresectable metastasis were included. The overall survival rate of these patients was 23.0%. However, the data of one study is not enough to draw a conclusion about the effect of treated or untreated lymph node metastasis on the five-year survival rate. When comparing patients with unilateral lymph node metastasis to patients with bilateral metastasis, our results show that there is no significant difference between these two groups in five-year survival rate. The Risk Ratio is 1.32, but the 95% Confidence Interval ranges from 0.92 to 1.88, so there is no significant evidence that there is a difference in Risk Ratio between the groups. It is important to keep in mind that unilateral lymph node metastasis does not imply that there is only one metastasis. Whether the metastasis are unilaterally or bilaterally distributed only indicates whether the metastases are positioned to the left or right of the median axis of the body, or on both sides. Bilateral lymph node metastasis per definition involves more than one lymph node. Therefore, this could be a

Table 2: *Summary of findings.*

	No lymph node metastasis		Lymph node metastasis			
Study	**Alive (%)‡**	**Total**	**Alive (%)‡**	**Total**	**Risk Ratio†**	**Comments**
Alcock et al. [4]	118 (84.9)	139	17 (40.5)	42	2.10 [1.44, 3.05]	Lymph node status of 33 patients unknown; 4 patients lost to follow-up
Atahan et al. [5]	57 (62.0)	92	15 (29.0)	52	2.15 [1.36, 3.39]	Lymph node status of 39 patients unknown
Girardi et al. [6]	227 (89.3)	254	95 (57.1)	166	1.56 [1.36, 1.79]	-
Hellebrekers et al. [7]	210 (91.0)	231	33 (53.0)	63	1.74 [1.37, 2.20]	14 patients excluded from the analysis of prognostic factors
Ho et al. [8]	132 (87.3)	151	31 (67.2)	46	1.30 [1.05, 1.60]	-
Hopkins et al. [9]	9 (47.0)	19	10 (21.8)	46	2.18 [1.05, 4.50]	OS+ only available for FIGO stage III; Low number of patients
Hosaka et al. [10]	294 (94.8)	310	67 (62.1)	108	1.53 [1.32, 1.78]	7 patients lost to follow-up
Inoue et al. [11]	552 (89.0)	620	148 (66.5)	223	1.34 [1.22, 1.48]	32 patients with unresectable metastasis (survival rate = 23.0%)
Ishikawa et al. [12]	126 (89.2)	141	21 (39.9)	52	2.21 [1.58, 3.09]	-
Liu et al. [13]	215 (91.0)	236	40 (67.0)	60	1.37 [1.14, 1.64]	-
Macdonald et al. [14]	3,381 (91.0)	3,715	546 (64.4)	848	1.41 [1.34, 1.49]	4 too many people in analysis (4563 instead of 4559)
Metindir et al. [15]	66 (89.2)	74	15 (83.3)	18	1.07 [0.86, 1.34]	Low number of patients
Nakanishi et al. [16]	410 (97.1)	422	69 (79.3)	87	1.23 [1.10, 1.37]	-
Tanaka et al. [17]	199 (91.9)	216	40 (42.1)	94	2.17 [1.71, 2.75]	-
Total	5,996 (90.6)	6,620	1,147 (60.2)	1,905	1.51 [1.38, 1.65]	

‡Total number of people alive after five years.† Risk Ratio for survival without lymph node metastasis, calculated by dividing survival rate "no lymph node metastasis" by survival rate "lymph node metastasis". +OS = overall survival.

Table 3: *Results for 5-year survival rate in patients with bilateral lymph node metastasis compared to patients with unilateral lymph node metastasis.*

Study	Unilateral lymph node metastasis		Bilateral lymph node metastasis		Risk Ratio [95% CI]
	Alive‡	Total	Alive‡	Total	
Liu et al. [13]	26	36	14	24	1.24 [0.83, 1.84]
Tanaka et al. [17]	19	64	5	30	1.78 [0.74, 4.31]
Total	45	100	19	54	1.32 [0.92, 1.88]

‡ Total number of people alive after five years. Risk Ratio for survival with unilateral metastasis, calculated by dividing survival rate "unilateral lymph node metastasis" by survival rate "bilateral lymph node metastasis".

Table 4: *Results for 5-year survival rate in patients with metastasis in one lymph node compared to patients with metastasis in more than one lymph node.*

Study	One lymph node involved		More than one lymph node involved		Risk Ratio [95% CI]
	Alive‡	Total	Alive‡	Total	
Girardi et al. [6]	36	52	55	107	1.35 [1.04, 1.74]
Ho et al. [8]	12	16	20	30	1.13 [0.77, 1.64]
Hosaka et al. [10]	42	45	25	63	2.35 [1.72, 3.22]
Inoue et al. [11]	79	98	69	125	1.46 [1.21, 3.22]
Metindir et al. [15]	5	5	10	13	1.22 [0.83, 1.80]
Nakanishi et al. [16]	37	38	32	49	1.49 [1.21, 1.84]
Tanaka et al. [17]	32	51	10	43	2.70 [1.51, 4.83]
Total	243	305	221	430	1.54 [1.27, 1.85]

‡Total number of people alive after 5 years. Risk Ratio for survival metastasis in one lymph node, calculated by dividing survival rate "one lymph node involved" by survival rate "more than one lymph node involved".

confounding factor in our analysis. When comparing patients with only one metastasised lymph node to patients with multiple metastasised lymph nodes, our results show that the former have a significantly higher five-year survival rate (RR of 1.54 and 95%CI 1.27;1.85). This implies that the number of affected lymph nodes influences the prognosis of patients with cervical cancer.

The choices we made in our research process could have affected the outcome of this study. We used a language filter to select the studies. All studies that were not written in English were excluded, because the time span of our research was too short to get a professional translation of the texts. This filter might have introduced selection bias in our systematic review. Furthermore, there were no full texts requested when no full text was available in Pubmed or Embase (or anywhere else on the Internet). We divided the 4,659 articles that had to be screened on title and abstract in five equal parts. Each of us screened one of those parts separately on inclusion and exclusion criteria. This could have led to selection bias. The included studies all used different methods to treat and remove the lymph node metastases. We did not subdivide the different methods of treatment in our analyses. There is a possibility that the prognosis differs between methods of treatment. Additionally, the studies in our review differ in included patients and their FIGO stage. Both can partly explain the high heterogeneity (75%, calculated by RevMan) of our studies. Despite the high heterogeneity we chose to calculate an overall risk ratio. This choice is based on the observation that all studies present a Risk Ratio in favour of the group without lymphatic metastasis. Finally, the critical appraisal was performed by two groups of either two or three people. Each group critically appraised half of the studies. They did not verify each other's work, which may have induced a misjudgement in the risk of bias.

In the studies 'Lymphatic metastasis versus no lymphatic metastasis', there are patients lost to follow-up. However, the number of patients lost to follow-up is small enough, in comparison to the number of patients included in these studies, to ensure that the outcome is not significantly affected by the missing data. The same goes for the study of Macdonald et al. [14], where four too many people were included in the analysis.

In the article of Hopkins et al. [9], the overall survival was only given for patients in FIGO stage III, while in the other articles overall survival was collectively given for multiple stages. This probably affected the number of patients alive after five years, because people in late stages of cancer are less likely to survive for a longer period of time.

Conclusion

The five-year survival rate in patients with cervical cancer and lymphatic metastasis is significantly worse in comparison to patients without lymphatic metastasis. We can also conclude that prognosis gets worse if more lymph node metastases are present. Therefore, it is essential to improve the diagnostic tools and treatment of lymph node metastases. Bilateral lymph node metastasis, in comparison to unilateral metastasis, seems to have a negative effect on the five-year survival rate of patients. However, this effect is not significant.

Further research is needed to elucidate the role of the location of the lymphatic metastases on the survival rate. This could be examined by carrying out a cohort study including patients with either unilateral or bilateral lymphatic metastasis.

Acknowledgements
We would like to thank Casper Tax, PhD, for his support and for providing insight and expertise during this study.

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