The Egyptian Journal of Otolaryngology

ORIGINAL ARTICLE Open Access

Correlation between the perineural invasion and neck metastasis in patients with laryngeal carcinoma: a cross sectional study

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Abstract

Background One of the most problematic issues of laryngeal carcinoma is recurrence after surgery one of the causes of recurrence this study tries to find its relevance is the peri neural invasion.

Aim of the work To determine whether there is a relationship between perineural invasion and cervical nodal metastases of laryngeal squamous cell carcinoma.

Methods Between December 2019 and September 2020, this study was conducted on 30 individuals who had laryngeal SCC. After the surgical removal of the tumor, a histological examination was done to check for the existence of perineural invasion, which was later linked to the cervical nodal metastases.

Results Of our patients 26.7% (8/30) had perineural invasion. Perineural invasion and cervical nodal metastasis were statistically significantly associated (*P* value = 0.018).

Conclusion A strong histologic predictor of cervical nodal metastases is perineural invasion.

Keywords Laryngeal squamous cell carcinoma, Perineural invasion, Nodal metastasis

Background

Every year, head and neck cancer accounts for around 6% of all new malignancies worldwide. Squamous cell carcinoma is the pathology diagnosis for the majority of head and neck cancer patients (SCC) [1]. The majority of fatalities from the tumor are caused by recurrence, in the primary site or the neck nodes [2], so it was critical to search for risk indicators for recurrence. Perineural invasion is one of these indicators.

It is not only a path of low resistance for cancer to spread within the nerve [2]. Malignancies can spread centripetally, and they are also able to form skip lesions [3, 4].

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In literature, there are many words that might be used carelessly, yet they represent different processes. The microscopic infiltration of the nerve fasicula is known as perineural invasion or small-caliber nerve invasion which is detected at the main site of the tumor, and it can be seen histopathologically. Perineural spread (PNS) or large-caliber nerve invasion is the gross shape, which is detected clinically or by the possible imaging modalities and is found beyond the main tumor lesion [2, 5]. Perineural growth can be generally used to refer to both PNI and PNS [6].

PNI is a well-known technique for tumor dissemination in a variety of human malignancies, such as adenoid cystic carcinoma of the salivary glands, pancreatic, prostate, and other types. The larynx can offer a model to investigate the possibility of PNI in the cases of laryngeal SCC for a lot of reasons; for example, stomal recurrence can be explained by metastases in the paratracheal lymph nodes, but another explanation for it is the cancer cells

remaining in the stumps of the nerves, which could be a source for the recurrence later [7]. Another reason is because the larynx's paired nerves can be easily detected, sacrified during laryngectomy, and histopathologically evaluated to determine whether PNI is present [8]. The aim of our work is to determine whether there is a relationship between perineural invasion and cervical nodal metastases of laryngeal squamous cell carcinoma.

Methods

Total sample size needed in this survey was 43 patients having laryngeal SCC, in the period from December 2019 to September 2020. The reporting guideline that has been followed in this study is the STROBE guideline. Sample size was calculated using the following formula:

$$\text{Sample size} = \frac{\frac{z^2 \times p(1-p)}{e^2}}{1 + \left(\frac{z^2 \times p(1-p)}{e^2 N}\right)}$$

N = population size • e = Margin of error (percentage in decimal form) • z = z-score

Also, margin of error was calculated using the following formula:

$$\textbf{Margin of error} = z \times \frac{\sigma}{\sqrt{n}}$$

n = sample size • σ = population standard deviation • z = z = score

The institutional review board of our department and institute has authorized the study by the date of 21/2/2017. Our patients should have a Pathological diagnosis of SCC of the larynx and be treated by surgery (either primary resection or salvage).

Prior to surgery, all patients underwent an evaluation protocol that included taking their medical history, undergoing a general and local physical examination, having a neck CT with intravenous contrast Fig. 1, and having a direct laryngoscopy to map out the primary tumor accurately and take a biopsy to confirm the diagnosis. Routine preoperative laboratory investigations were done. Written consent is taken from all the patients prior to surgery. Surgical resection of the primary tumor either by doing total or partial laryngectomy besides the management of the cervical lymph nodes was performed, then the histopathological examination was performed in the pathology department of our institute.

The specimens underwent routine processing in preparation for histological analysis. Hematoxylin and Eosin was used to prepare and stain the sections. The pathologist analyzed the samples to look for PNI in large (such as the superior and recurrent laryngeal nerves) or small nerves Fig. 2.

In patients, whose histopathological examination revealed PNI, this was correlated to cervical nodal metastasis (a pathological finding).

Results

Gender distribution

Gender distribution among surveyed patients was presented in Table 1 and Fig. 3. Comparisons between male and female was performed by using Chi square test which revealed that male (93.3%) was significantly higher than female (6.7%) as $P < 0.05$.

N staging distribution

Frequency and percentages of N stages distribution among surveyed sample was presented in Table 2 and Fig. 4. Comparison between different stages was performed by using Chi square test which revealed significant difference between different stages as $P < 0.05$, as N0 (65.11%) was significantly the highest, while N3 (2.33%) was significantly the lowest.

Perineural invasion distribution:

Frequency and percentages of patients with + ve and -ve perineural invasion among surveyed patients were presented in Table 3 and Fig. 5. Comparison between + ve and -ve was performed by using Chi square test which revealed that + ve (25.58%) were significantly lower than -ve (74.42%) as $P < 0.05$.

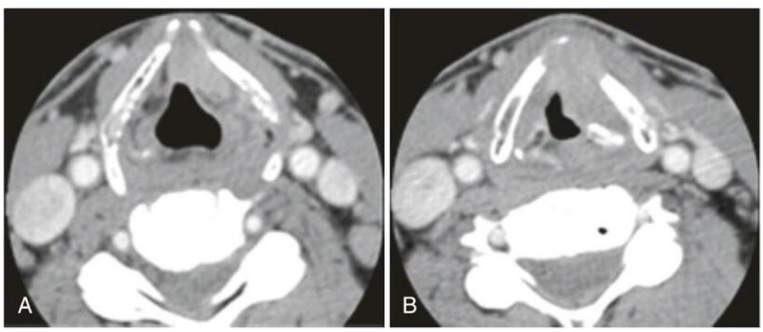

Fig. 1 CT neck with IV contrast showing glottic, supraglottic laryngeal SCC, with thyroid cartilage invasion, T4aN1M0

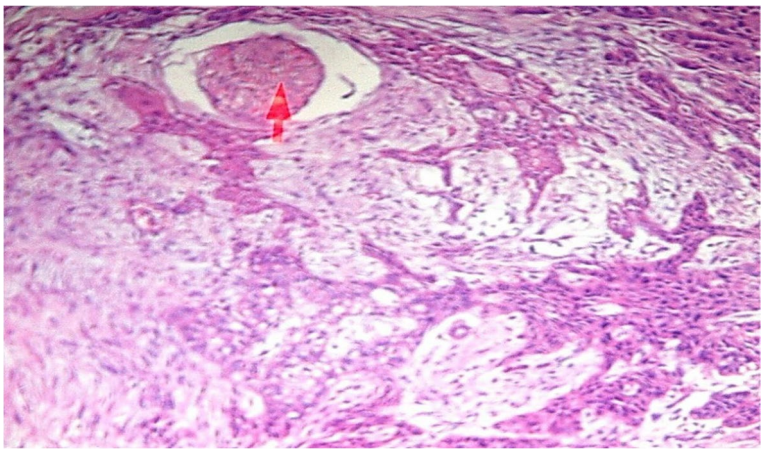

Fig. 2 Histopathological examination of the same patient, showing PNI (the red arrow)

Table 1 Frequency and percentages of gender distribution among surveyed patients

Gender	N	%	Chi square test		
			P value	95% CI	
				L	U
Male	40	93.30%	< 0.0001*	70.2	92.8
Female	3	6.70%			

N: frequency, %: Percentage

* Significant difference as $P < 0.05$

Table 2 Frequency and percentages of N staging among surveyed patients

N stage	N	%	*P* value
N0	28	65.11	< 0.0001*
N1	10	23.26	
N2	4	9.30	
N3	1	2.33	

N: frequency, %: Percentage

* Significant difference as $P < 0.05$

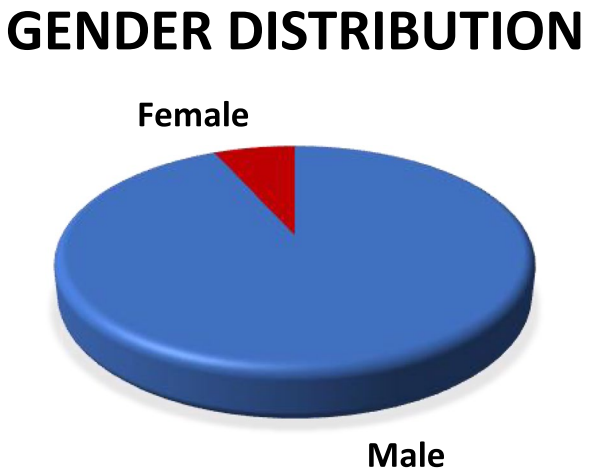

Fig. 3 Pie chart showing gender distribution among surveyed patients

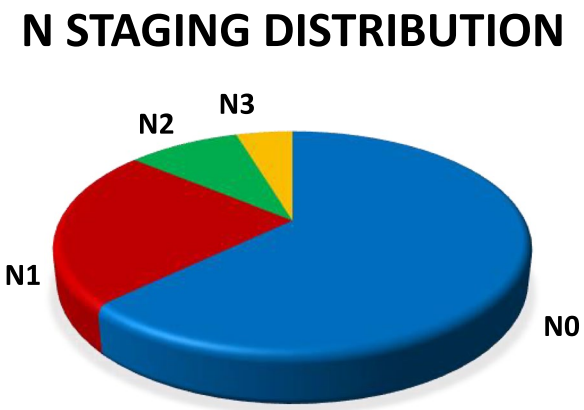

Fig. 4 Pie chart showing N staging distribution among surveyed patients

Distribution of N staging among PNI

Distribution of N staging among PNI was presented in Table 4 and Fig. 6. Comparison between + ve and -ve PNI in each N stage was performed by using Chi square test which revealed significant difference between them only in N0 as -ve (89.2%) was significantly higher than + ve (10.71%), while there was insignificant difference between them in all other stages.

Distribution of T staging among PNI

One patient (16.7%) of those having T1 laryngeal SCC was + ve for PNI, 1 patient (20%) of those having T2

Table 3 Frequency and percentages of perineural invasion among surveyed patients

PNI	N	%	Chi square test		
			P value	95% CI	
				L	U
+ve	11	25.58%	< 0.0001*	28.1	63.9
-ve	32	74.42%			

N: frequency, %: Percentage

* Significant difference as $P < 0.05$

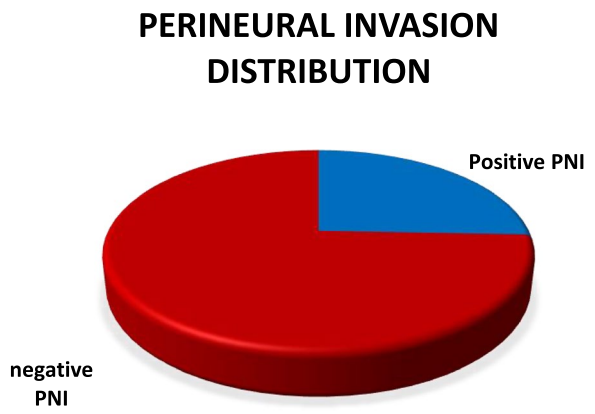

Fig. 5 Pie chart showing perineural invasion distribution among surveyed patients

laryngeal SCC was + ve for PNI, 3 patients (42.9%) of those having T3 laryngeal SCC were + ve for PNI and finally 3 patients (25%) of those having T4 laryngeal SCC were + ve for PNI, as shown in Table 5. From these results, we conclude that there is no statistical significance of the T stage of laryngeal SCC and the perineural invasion.

Discussion

TNM staging, which is based on the physical examination, imaging investigations, and histological characteristics of the specimen, is used to determine the course of treatment and the prognosis for head and neck SCC [9]. Numerous studies have demonstrated how important PNI is as a risk factor for individuals with head and neck SCC. The overwhelming body of research shows that PNI is a reliable indicator of the presence of concealed cervical nodal metastases [10].

In contrast to Fagan et al., who detected PNI in 52 percent of their patients, we discovered in our study that the prevalence of PNI in our patients was 26.7 percent [11] this difference occurs because we concentrate in our study on patients with laryngeal carcinoma while Fagan study concentrate on the whole aerodigestive tract.

In agreement with our findings, Tai et al. reported on 307 patients with head and neck squamous cell carcinoma at various sites and found that PNI was an independent predictor of cervical nodal metastases, even in early-stage tumors. This study concluded that there is a statistically significant relationship between the PNI of the SCC of the larynx and the cervical nodal metastasis [12], and Miller et al. showed that PNI was linked with the quantity of the cervical nodes that were malignant [13]. To avoid underestimating the neck status, it should be taken into account that Ross et al. showed that PNI was a good histologic predictor of cervical nodal metastases [10].

Fagan et al. conducted a clinicopathological analysis on 142 patients who underwent primary surgical resection of SCC at several sites in the head and neck, including the oral cavity, oropharynx, larynx, and hypopharynx, between 1981 and 1991. Contrary to our findings, this investigation demonstrated an association between PNI and nodal metastases that were histopathologically identified, but only with carcinoma of the oropharynx and oral cavity (P value = 0.03) and not with carcinoma of the larynx or hypopharynx (P value = 0.75) [11] these results occurs because exralaryngeal tumours had relatively higher incidence of nodal and extranodal spread.

In line with our investigation, Balci et al. performed a retrospective analysis using information from 110 laryngectomy cases and neck dissection specimens. The

Table 4 Distribution of N stage (nodal metastasis) among PNI the of laryngeal SCC

N staging	Total N	PNI				
		+ve		-ve		*P* value
		N	%	N	%	
N0	28	3	10.71%	25	89.29%	< 0.0001*
N1	10	4	40.00%	6	60.00%	0.38
N2	4	3	75.00%	1	25.00%	0.18
N3	1	1	100.00%	0	0%	0.31

N: frequency, %: Percentage

* Significant difference as $P < 0.05$

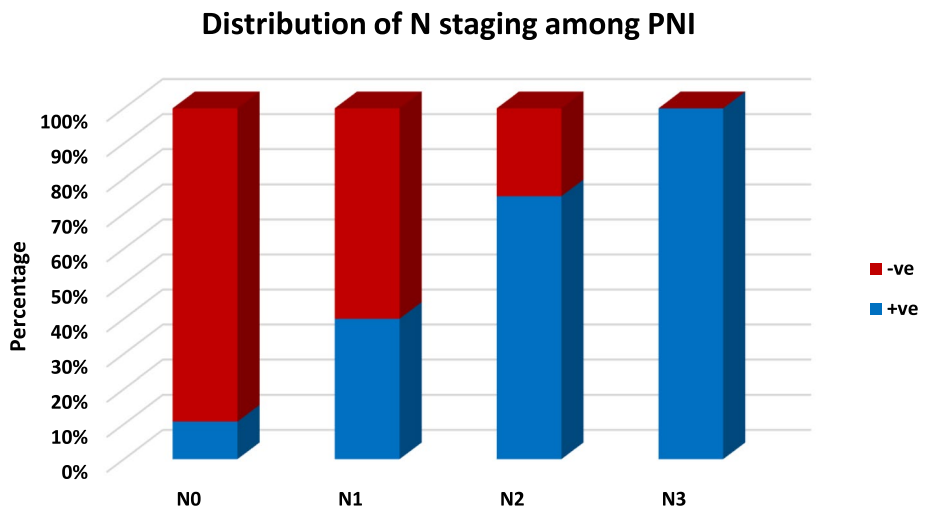

Fig. 6 Stacked bar chart representing distribution of N staging among PNI

Table 5 Correlation between PNI and the T stage of laryngeal SCC

	T Staging								*P* value
	T1		T2		T3		T4		
	N	%	N	%	N	%	N	%	
PNI									
+ ve	1	16.7%	1	20.0%	3	42.9%	3	25.0%	0.796
-ve	5	83.3%	4	80.0%	4	57.1%	9	75.0%	

N: frequency, %: Percentage

* Significant difference as $P < 0.05$

findings revealed a strong association between PNI and cervical nodal metastases [14], and this result is also compatible with several studies in the literature [2].

In multivariate models, PNI has also been demonstrated to be a marker of advanced disease [15]. This is one of the criteria surgeons use to determine whether adjuvant radiotherapy is necessary [16]. With PNI, other series have noted an elevated incidence of regional recurrence [10].

Future research examining more PNI patients may offer more accurate risk categorization and new treatment approaches. We are able to stratify the actual risk of locoregional recurrence thanks to the early detection of PNI in laryngeal SCC. To identify patients who are more at risk and to improve the ability to moderate the processes of PNI in laryngeal SCC, a deeper understanding of the molecular mechanisms of PNI is also required.

Recommendations:

It is essential to have pretreatment PNI prediction strategies. Predicting perineural growth can benefit greatly from the use of MRI, CT, PET-MRI, PET-CT and diffusion tensor imaging. To detect perineural invasion, however, an ordinary frozen section is advised intraoperatively. These techniques are crucial because failing to identify perineural development before surgery could have serious consequences. A tumor recurrence, as opposed to a recurrence, is practically guaranteed in the event of such failure.

PNI is regarded as a strong histologic predictor of cervical lymph node metastases because laryngeal SCC's propensity to metastasize to the neck lymph nodes is significantly correlated with it. As a result, it is strongly advised to perform elective neck dissection in PNI-positive, clinically node-negative tumors. In the histopathology reports, we suggest that PNI be frequently recorded. We observe that PNI can be incorporated into the laryngeal cancer TNM stage.

Conclusion

In cases of laryngeal SCC, PNI and cervical nodal metastases (N stage) are correlated. Therefore, if PNI is identified either intraoperatively by frozen section or preoperatively by the various imaging modalities, neck dissection should be carried out.

Acknowledgements
Not applicable.

Authors' contributions
MA was mainly involved in doing the surgical part of the research. AB designed the work, the acquisition, analysis, interpretation of data. FG prepared the patients preoperatively and followed their up postoperatively and was responsible for following and obtaining the pathology. All the authors approved the submitted version.

Funding
This work has no fund.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
• Each patient completed an informed consent form before taking part in the research. The research protocol also approved by ethical committees.
• The ENT department-Faculty of Medicine-Cairo university ethics committee and kasr AlAiny school of medicine ethics committee approved the research protocol.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 21 October 2022 Accepted: 14 April 2023
Published online: 01 May 2023

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