Rev Colomb Cir. 2021;36:599-610
https://doi.org/10.30944/20117582.853

ORIGINAL ARTICLE

Impact of the node-stage migration phenomenon on survival and recurrence of patients with papillary thyroid cancer who underwent prophylactic lymph node dissection

Impacto del fenómeno de migración de estadio ganglionar en la supervivencia y la recurrencia de pacientes con cáncer papilar de tiroides sometidos a vaciamiento ganglionar profiláctico

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Abstract

Introduction. The role of prophylactic central lymph node dissection at the time of total thyroidectomy remains controversial in clinically node-negative (cN0) papillary thyroid carcinoma. Moreover, a prospective randomized controlled trial of prophylactic central lymph node dissection in cN0 PTC is not readily feasible.

Methods. In this study, we simulated cN0 and clinically node-positive (cN+) populations, to evaluate impact of nodal stage migration in papillary thyroid carcinoma patients that undergo prophylactic central neck dissection. We use simulations of population and nodal stages.

Results. Nodal stage migration phenomenon had a spurious improvement effect in locoregional recurrence and overall survival of cN0 and cN+ populations, without changes in overall population and individual outcomes.

Discussion. Nodal stage migration is recognized as an important bias that precludes the use of historical controls groups in experimental treatment trials. In accordance to our findings, this phenomenon could explain the improvements observed in outcomes in patients that undergo prophylactic central neck dissection.

Keywords: papillary thyroid cancer; lymph node excision; nodal stage migration; central neck dissection; local neoplasm recurrence; survival.

Received: 09/15/2020 - Accepted: 11/15/2020 - Date of publication online: 06/10/2021
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Cite as: Agamez-Fuentes JE, Sanabria AE. Impacto del fenómeno de migración de estadio ganglionar en la supervivencia y la recurrencia de pacientes con cáncer papilar de tiroides sometidos a vaciamiento ganglionar profiláctico. Rev Colomb Cir. 2021;36:599-610. https://doi.org/10.30944/20117582.853

Resumen

Introducción. Dado que un ensayo clínico aleatorio es irrealizable, el rol del vaciamiento ganglionar profiláctico en pacientes con cáncer papilar de tiroides sin comprobación clínica de compromiso ganglionar metastásico (cN0) es controversial. El vaciamiento ganglionar profiláctico acarrea un proceso de reclasificación de pacientes, al hacer evidente la positividad ganglionar micrometastásica antes ignorada, lo que genera una aparente pero falsa mejoría en los desenlaces de los grupos de estadificación, mientras el pronóstico individual y total de la población no cambia, fenómeno conocido como migración de estadio o fenómeno de Will Rogers.

Métodos. Se ejecutaron simulaciones de poblaciones con cáncer papilar de tiroides con compromiso ganglionar metastásico clínicamente evidente (cN+) y cN0, para determinar el impacto del fenómeno de migración de estadio en los pacientes sometidos a vaciamiento ganglionar profiláctico.

Resultados. Con la simulación de las poblaciones y sus estadios ganglionares, se observa cómo la migración de estadio ganglionar genera una aparente mejoría en los desenlaces de recurrencia loco regional y supervivencia, sin cambiar los desenlaces de la población total ni individuales.

Discusión. El fenómeno de migración de estadio es uno de los sesgos más importantes que limitan el uso de grupos históricos de control en ensayos de tratamiento experimental. De acuerdo con nuestros resultados, este fenómeno podría explicar los beneficios observados con el vaciamiento ganglionar profiláctico en algunos de los estudios agregativos publicados hasta el momento, hallazgos que no han sido documentados para el cáncer papilar de tiroides.

Palabras clave: cáncer papilar tiroideo; escisión del ganglio linfático; migración de estadio ganglionar; disección del cuello central; recurrencia local de neoplasia; supervivencia.

Introduction

Thyroid cancer is the most common endocrine neoplasia. Between 85 and 95% of patients with thyroid neoplasms have papillary thyroid cancer (PTC), which has a high long-term survival. Surgery, radioactive iodine and thyroid hormone suppression are the mainstays of current management of PTC [1-3].

Due to the lack of prospective controlled studies, many of the recommendations in the management guidelines regarding the extent of surgery, the role of radioactive iodine in the treatment of low-risk patients, the timing and frequency of surveillance are controversial [1].

Regarding surgery, there is a consensus that lymph node dissection should be performed in the presence of palpable lymphatic involvement or detected by images, which has been called therapeutic dissection, and may include the central or lateral compartment of the neck. However, in patients with clinical stage N0 (cN0), it is not clear about the role of prophylactic central lymph node dissection.

Regional lymphatic metastases, in thyroid cancer patients, have been shown to impact regional local recurrence (RLR) and mortality. However, in cN0 cases the effect of existing micrometastases on the outcomes of these patients is not clear. Furthermore, routine lymph node dissection can lead to increased complication rates, including permanent hypoparathyroidism and recurrent laryngeal nerve injury [1,2].

It is clear that survival is much worse in patients with regional metastatic disease than in patients with localized disease. Due to the precision of the new methods, patients with micrometastases, previously classified in the group of localized tumors, are now classified as patients with regional metastatic disease, as the previously undetectable micrometastatic tumor burden is evident. These patients with a small metastatic tumor burden have better survival rates than patients with massive metastatic processes, but worse survival rates than patients with non-metastatic cancer. For this reason, its transfer from the localized cancer group to the metastatic cancer group can increase survival in both groups, wi-

thout changing the survival of each individual in particular, or of the total population with cancer. This epidemiological paradox is known as the stage migration phenomenon or the Will Rogers phenomenon [4-6].

Our hypothesis is that the Will Rogers phenomenon is mediating the apparent increases in survival and the decrease in the recurrence rates of patients undergoing prophylactic central lymph node dissection in cN0 thyroid cancer, as has already been demonstrated in other tumors. such as lung, stomach and colorectal cancer [7-12].

Therefore, our research question posed is: When comparing adult patients with papillary thyroid cancer who underwent total thyroidectomy and prophylactic central lymph node dissection with patients who underwent total thyroidectomy, does the phenomenon of stage migration explain the increase in survival of the staging subgroups?

To find the solution to this question, a randomized clinical trial would be necessary to compare the performance of prophylactic central lymph node dissection or not in patients with stage cN0 PTC. However, the sample size would be close to 5,840 patients and it will require too long a follow-up time and unacceptable costs for a health system, which is why this trial has been considered unfeasible [1].

Another alternative for solving this clinical question is the design of a mathematical model with population parameters, where it is possible to simulate the population distribution of tumor lymph node stages, to systematically evaluate the effect of ganglion stage migration in the survival of patients with papillary thyroid cancer who are taken to prophylactic central lymph node dissection and compare survival rates with the group of patients who did not undergo such procedure.

Methods

Design: This is a secondary mathematical model study based on parameters extracted from the literature.

Search for primary sources: The study population was adult patients with well-differentiated papillary thyroid cancer, with no clinical or imaging evidence of metastatic lymph node involvement (cN0).

The MEDLINE database was searched for studies published in the last 20 years regarding prophylactic central lymph node dissection in papillary thyroid cancer. Articles published in English were included evaluating prophylactic central lymph node dissection in papillary thyroid cancer, the RLR rate, and survival in the different staging groups. Articles that did not mention the proposed outcomes (RLR and survival in the different staging groups) were excluded. In Annex 1, is shown the search strategy used in PubMed for the review of potentially relevant articles.

Generation of the cN0 population and the distribution of patients with micrometastasis: From the data obtained, a hypothetical population of cN0 patients was generated, possessing the distribution of the risk factors identified in the literature (sex, age, multifocality, tumor size, location, lymphovascular invasion, extrathyroid extension, capsular invasion) [4,5].

The data extracted for the model can be seen in table 1. To assign these risk factors, binomial probability distributions were used with the parameters defined by the selected studies. Annex 2 describes the generic simulation strategy that was used for each of these parameters in the STATA software.

Once said population was defined, the possibility of micrometastasis was determined. For this step, the standard gamble method was used and a cut-off point was defined in 3 risk factors. Any patient with more than three risk factors present was considered positive for micrometastases. As proof of the accuracy of the model, the prevalence of risk factors and the presence of micrometastases was determined and compared with the results of the literature.

Generation of the cN+ population: The population with clinically positive lymph nodes was generated from the studies of Kim et al. [13] and the meta-analysis by Zhao and Li [14], who reported the frequency of suspicious lymph nodes by ultrasound, adjusting for the proportion of false positives (Table 1).

Table 1. Parameters extracted for model generation.

Parameter	Value	Source	Observations

Sex:
a: Male
b: Female
rda: nodal compromise for a
rdb: nodal compromise for b
	pa=0,149;
	rda=0,5892;
	rdb=0,4711
		Sun et al., 2015 [5]	14.9% male, with 58.9% of micrometastasis

Age:
c: Age < 45 year-old
d: Age > 45 year-old
	pc=0,474;
	rdc=0,4616;
	rdd=0,3448
		Sun et al., 2015 [5]	

Multifocal:
e: Multifocal tumor
f: Focal tumor
	pe=0,259;
	rde=0,5358;
	rdf=0,4703
		Sun et al., 2015 [5]	

Tumor size:
g: > 2 cm
h: < 2 cm
	pg=0,369;
	rdg=0,7212;
	rdh=0,4790
		Sun et al., 2015 [5]	

Tumor location:
i: Central area and lower pole
j: Upper pole
	pi=0,722;
	rdi=0,4672;
	rdj=0,3181
		Sun et al., 2015 [5]	

Lymphovascular invasion:
k: Positive
l: Negative
	pk=0,238;
	rdk=0,5771;
	rdl=0,3378
		Sun et al., 2015 [5]	

Extrathyroid extension:
m: Positive
n: Negative
	pm=0,231;
	rdm=0,5138;
	rdn=0,4852
		Sun et al., 2015 [5]	

Capsular Invasion:
o: Positive
p: Negative
	po=0,206;
	rdo=0,5419;
	rdp=0,3714
		Sun et al., 2015 [5]	

PPV of ultrasound in the detection of positive nodes	VPP 86%	Kim et al., 2008 [13] Zhao and Li [14]	With this data that the proportion of cN+ patients that are pN0 is obtained.
Proportional relationship between the cN0 and cN+ populations	- cN+: 9.3% of the population - cN0: 90.7% of the population	Wada et al., 2003 [6]	
Proportion of stages in cN+ with pN+	pN1a: 99 / (99 + 130) = 42% pN1b: 130 / (99 + 130) = 58%	Nixon et al., 2014 [10]	With this data, the overall RLR-free survival of cN+ patients with pN+ is weighted.
Proportion of stages in cN0 with pN+	pN1a: 60 / (60 + 73) = 45% pN1b: 73 / (60 + 73) = 55%	Hartl et al., 2012 [19]	
5-year RLR-free survival	pN0: 99% pN1a: 93% pN1b: 90% Global cN+ pN+ = 0,9126 Global cN0 pN+ = 0,9135	Nixon et al., 2014 [10]	
10-year RLR-free survival	pN0: 96% pN1a: 88% pN1b: 85% Global cN+ pN+ = 0,8626 Global cN0 pN+ = 0,8635	Nixon et al., 2014 [10]	
Overall survival at 10 years	N0: 98% N1a: 92% N1b: 94% Global cN+ pN+ = 0,9316 Global cN0 pN+ = 0,9310	Vrachimis et al., 2015 [20]	

Proportion between the cN0 and cN+ populations: The distribution of the cN0 and cN+ populations was obtained from the study by Wada et al. [6]. Finally, the population was segmented based on its lymph nodes stages as shown in figure 1.

Simulation of outcomes: The distribution of outcomes (RLR and survival) was based on the variable lymph node metastasis, using the risk percentages according to the lymph node staging reported in the literature. These distributions were binomial. Figure 2 shows a process diagram of the generation of populations, outcomes and comparison of the proposed scenarios.

Statistic analysis

With these generated populations, comparisons were made in scenarios of migration and non-migration of the lymph node stage, to compare the outcomes of RLR and survival, between populations taken to lymph node dissection and populations without dissection. The chi square test was used for categorical variables and the Student's t test for continuous variables. A value of $p < 0.05$ was considered statistically significant. Stata® software, version 14 (StataCorp. LP, College Station, TX, USA) was used for all simulations and analyzes.

Results

Table 1 describes the parameters extracted for the simulation model with their source. A total of 1,000,000 observations were simulated.

Regional recurrence outcome

According to Ryu et al [15], the risk of RLR in cN0 patients with pN1a was 5.7% at 6.5 years of follow-up. According to Hwangbo et al [16], the risk of total recurrence at 5 years and 10 years was 1.4% and 2.9% in pN0 patients, 6.0% and 12.2% in pN1a patients and 11.4% and 19, 3% in pN1b patients. Nixon et al [17] reported a regional loco recurrence-free survival at 5 and 10 years as follows: 99% and 96% for pN0 patients; 93% and 88% in pN1a patients, and 90% and 85% in pN1b patients, while in another study by Nixon et al [18] reported patients in pN1 stages with a 5-year central lymph node recurrence-free survival of 96.4%, and a 5-year recurrence-free survival rate of 91%. The results of Ryu et al [15], Hwangbo et al [16] and Nixon et al [17] reported very similar RLR frequencies in the cN0 and cN+ groups at 5 years,

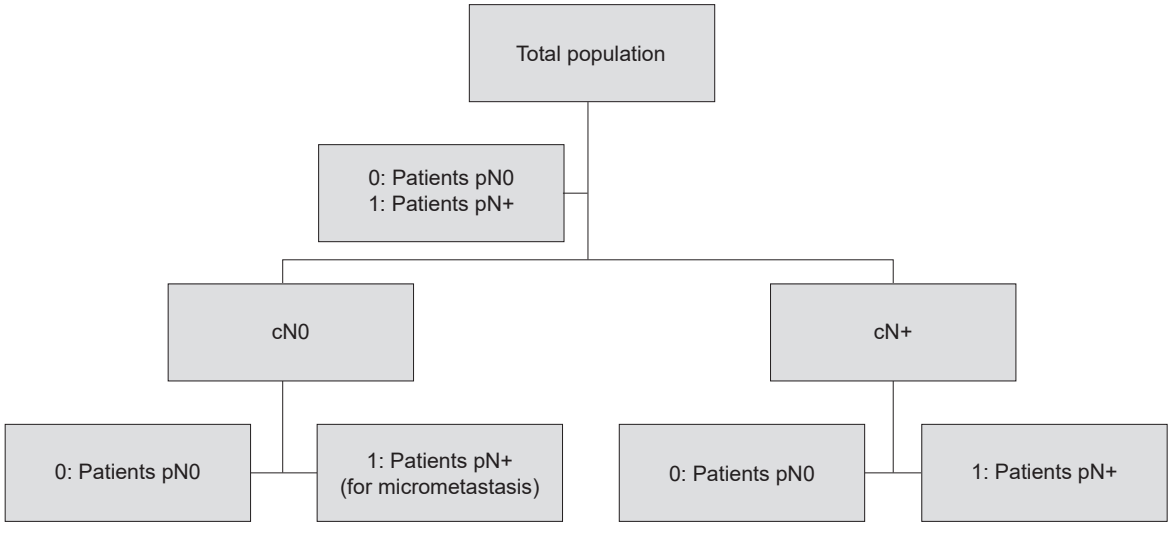

Figure 1. Final distribution of the hypothetical population in the lymph node dissection scenario. In the no-dissection scenario, the cN0 population is not discriminated since no lymph node histopathological study is performed.

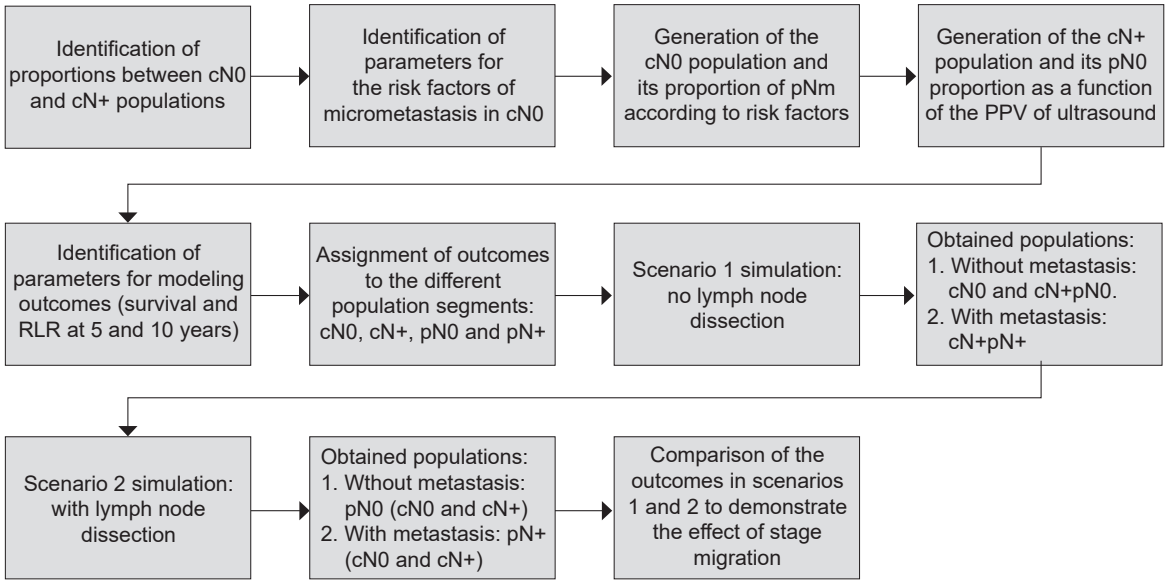

Figure 2. Process diagram of the generation of populations, outcomes and comparison of the proposed scenarios.

when the pathological stage is pN1a (5.7%, 6% and 7%), so it was considered that the recurrence rate would be the same for the same pathological stage.

The comparison between the studies by Wada et al [6], Kim et al [13], Nixon et al [17] and Hartl et al [19], showed that the proportions of the lymph node stages are different between cN0 and cN+ patients. In cN0 patients, the pN0 percentages are between 40-60%, while the pN0 percentages in cN+ patients is close to 14%. According to Nixon et al [17], the proportion of stages in cN+ patients is close to 42% for stages pN1a and 58% for stages pN1b. Finally, according to Hartl et al [19], the proportion of stages in cN0 patients with lymph node positivity on histopathological study is close to 45% for pN1a stages and 55% for pN1b stages.

Overall survival outcome

Vrachimis et al [20], reported an overall survival at 10 years according to the lymph node stage as follows: 98% for N0, 92% for N1a and 94% for N1b.

CN+ population, cN0 based on risk factors and total population

The prevalence of micrometastatic involvement was 55%, which is compatible with the different reports in the literature [4-6]. The population distribution was as follows: 9.27% of the patients are cN+ and 90.73% of the patients are cN0.

Table 2 shows the characteristics of the total simulated cN0 population according to their risk factors. The number of observations of the cN0 population was 907,300 and that of the cN+ population was 93,700, for a total population universe of 1,000,000 observations.

The lymph node involvement of both populations (cN0 and cN+) can be seen in table 3.

Analysis of migration

The initial scenario in which no prophylactic central dissection is performed in any patient is shown in Table 4. In the scenario where prophylactic lymph node dissection is performed and the population is redistributed according to their

Table 2. Characteristics of the total simulated population cN0 (907,300 observations).

Variable	Values	Observations	Percentage
Sex	0. Female	772.503	85,1
	1. Male	134.797	14,9
Age	0. Age > 45 year-old	476.774	52,5
	1. Age < 45 year-old	430.526	47,5
Multifocal	0. Focal tumor	671.613	74,0
	1. Multifocal tumor	235.687	26,0
Tumor size	0. < 2 cm	573.014	63,2
	1. > 2 cm	334.286	36,8
Tumor location	0. Upper pole	251.895	27,8
	1. Central are and lower pole	655.405	72,2
Lymphovascular invasion	0. Negativa	690.526	76,1
	1. Positiva	216.774	23,9
Extrathyroid extension	0. Negativa	698.152	76,9
	1. Positiva	209.148	23,1
Capsular invasion	0. Negativa	719.828	79,3
	1. Positiva	187.472	20,7

Table 3. Population segments and their lymph node stages.

Population segment	Nodal involvement	Observations	Percentage
cN0	0. pN0	415.871	45,8
	1. pN1	491.429	54,2
cN+	0. pN0	12.876	13,9
	1. pN1	79.824	86,1
Total		1.000.000	100

lymph node stage, patients with lymph node positivity (micro and macrometastasis) are assigned to the cN+ group. The epidemiological paradox of Will Rogers is then observed, with an apparent increase in RLR-free survival and overall survival at 10 years in the cN0 group, while the outcomes of the cN+ population segment vary minimally and in the general population remain unchanged, while the count of individuals suffering a certain outcome remains unchanged. This is clearly evidenced in table 5. Figure 3 shows the population distribution in both scenarios.

Discussion

The Will Rogers phenomenon is recognized as one of the most important biases limiting the use of historical control groups in experimental treatment trials. This is due to the fact that the use of different criteria or diagnostic tools can generate false improvements in the outcomes of the groups of patients, which can be erroneously interpreted as treatment effects [7,10].

The observation of an increase in the proportion of patients with lymph node positivity over time is known as nodal stage migration. If this phenomenon is accompanied by a constant T-stage distribution, there is the potential for a paradoxical improvement in survival in node-positive and node-negative groups, without an increase in overall survival or in individual patients [11].

This paradox is in contrast to the generally accepted perception that new staging technologies generally result in earlier detection and improved treatments, for example of lymph node metastases, leading to improved overall survival. This form of reclassification is well known in the oncology literature, and generally occurs

Table 4. Outcomes for both population segments in the scenario of not performing prophylactic lymph node dissection.

Population segment	Nodal involvement	5-year RLR-free survival	10-year RLR-free survival	10-year Overall survival	Total population
cN0	NA	860.521 (94,8%)	824.071 (90,8%)	864.906 (95,3%)	907.300
cN+	0. pN0	12.766 (99,1%)	12.367 (96,1%)	12.634 (98,1%)	12.876
	1. pN+	72.767 (91,2%)	68.731 (86,1%)	74.364 (93,2%)	79.824
Total: cN0 y cN+pN0		873.287 (94,9%)	836.438 (90,9%)	877.540 (95,4%)	920.176
Total population		946.054 (94,6%)	905.169 90,5%	951,904 95,2%	1.000.000

Note: the cN+ population segment that did not show metastatic involvement in the pathology is reassigned to the cN0 segment. There are no data on lymph node involvement in the cN0 group, since no prophylactic lymph node dissection was performed in this simulation scenario.

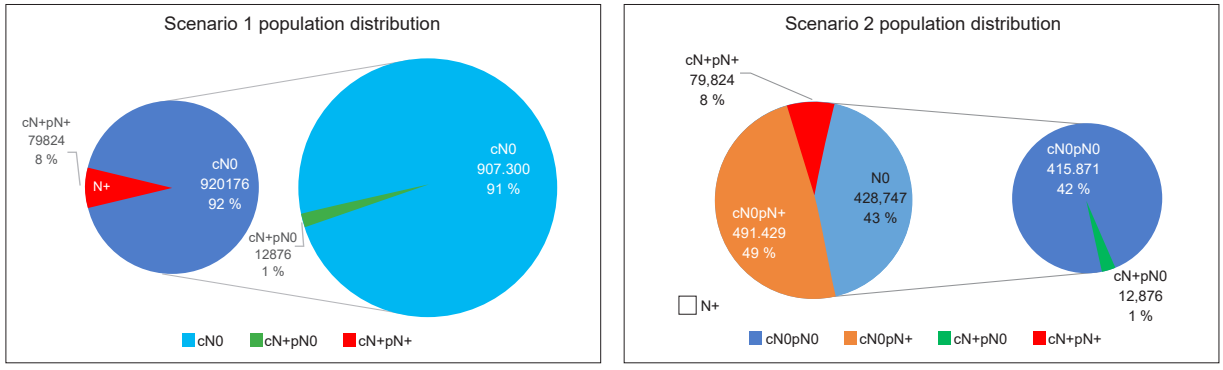

Figure 3. Simulated populations in the no-dissection scenario (scenario 1) and prophylactic lymph node dissection (scenario 2), respectively.

after the introduction of new imaging methods, but it has never been evaluated for prophylactic lymph node dissection in papillary thyroid cancer, which may play a role in reclassifying the patients, making evident the previously ignored lymph node positivity.

In this article, a population of papillary thyroid cancer patients has been simulated based on their risk factors. As previously published, prevalences of micrometastatic involvement have been defined for cN0 patients, as well as a population of cN+ patients. According to these data, a distribution of lymph node stages could also be assigned, where it was evidenced that the relationships between stages pN1a and pN1b were similar, both for the cN0 population segment and for cN+ patients, 45:55 and 42:58, respectively [17,19]. On the other hand, the great difference in the distribution of lymph node stage is found in the proportion of pN0 patients in the cN0 and cN+ populations, which corresponded to 45.8% and 13.8%, respectively (Table 3).

It is interesting to note that, in the light of the literature, there is insufficient evidence to affirm that the outcomes of patients with micrometastatic lymph node involvement (pNm) are different from those with clinically evident lymph node involvement (cN+), in terms of survival. free of loco regional recurrence [15,16,17].

When both scenarios are simulated, taking the population to prophylactic lymph node dissection, which implies its re-staging, or without performing it, the impact of lymph node stage migration on the outcomes of RLR-free survival and overall survival is observed.

In the first scenario, without prophylactic lymph node dissection, RLR-free survival at 5 years and 10 years and overall survival at 10 years of the N0 group (which includes cN0 and cN+ patients but without metastases in the pathological study: pN0), are 94.9%, 90.9% and 95.4%, respectively, while these same outcomes for the cN+ population segment are 91.1%, 86.1% and 93.2%, respectively. The differences between all the outcomes of both groups reached statistical significance when comparing the proportions with the chi-square test, with a $p<0.05$.

In the second scenario, using the same population and adding prophylactic lymph node dissection and the consequent re-staging, we observe that the entire cN0 pN+ group passes to the cN+ group, thus configuring a RLR-free survival at 5 years and at 10 years and overall survival at 10 years, for the pN0 group of 99.0%, 96.0% and 98.0%, respectively, while these same outcomes for the pN+ population segment, in which the cN0 pN+ group is now included, is 91.6%, 86.6% and 93.2%, respectively. The differences between all the outcomes of both groups reached statistical significance when comparing the proportions with the chi-square test, with a $p<0.05$.

When calculations of RLR-free survival at 5 years and 10 years and overall survival at 10 years, for the total population in the second scenario, there are no variations at all, and the observation counts also do not vary for any of the outcomes, as evidenced in table 5.

With this second scenario, an improvement in the outcomes of the N0 group (pN0 in the second scenario) after dissection and re-staging of the population, of 94.9%, 90.9% and 95.4% is evident at 99.0%, 96.0%, and 98.0% for RLR-free survival at 5 years and at 10 years and overall survival at 10 years, these differences are also significant when comparing the proportions with the chi-square test , with a $p<0.05$.

When comparing the decrease in risk in both groups of N0 patients in the described scenarios, an absolute decrease in the risk of RLR at 5 years and at 10 years of 4.1 and 5.2%, respectively, is found, which is a similar value to that reported in the literature of 3.9 and 6.9% [21,22].

Furthermore, the incidence of RLR in cN0 patients at 5 years is close to 1%, which is corroborated in other retrospective studies of prophylactic lymph node dissection in cN0 patients [23].

When analyzing the N+ group in both scenarios, it is found that the changes are minimal, from 91.2%, 86.1% and 93.2% to 91.6%, 86.6% and 93.2%, respectively, For each of the outcomes evaluated, and when performing the chi-square test

Table 5. Outcomes for both population segments with prophylactic lymph node dissection and stage migration of the pN1 from the cN0 group to the cN+ group.

Population segment	Nodal involvement	5-year RLR-free survival	10-year RLR-free survival	10-year Overall survival	Observations
cN0	0. pN0	411.771 (99,0%)	399.301 (96,0%)	407.,490 (98,0%)	415.871
	1. pN+	448.750 (91,3%)	424.770 (86,4%)	457.416 (93,1%)	491.429
cN+	0. pN0	12.766 (99,1%)	12.367 (96,1%)	12.634 (98,1%)	12.876
	1. pN+	72.767 (91,2%)	68.731 (86,1%)	74.364 (93,2%)	79.824
Total pN0		424.537 (99,0%)	411.668 (96,0%)	420.124 (98,0%)	428.747
Total pN+		521.517 (91,3%)	493.501 (86,4%)	531.780 (93,1%)	571,253
Total		946.054 (94,6%)	905.169 (90,5%)	951.904 (95,2%)	1.000.000

of statistical significance, with a p<0.05, there was only a statistically significant improvement in the 10-year locoregional recurrence-free survival outcome. On the other hand, the 5-year locoregional recurrence-free survival and overall survival did not show statistically significant changes.

Finally, when reviewing the number of observations in each scenario and the total percentages of the entire population in both scenarios, these do not change at all and remain in 946,542 (94.6%) subjects without RLR at 5 years, 904,933 (90,5%) subjects without RLR at 10 years and 951,904 (95.2%) subjects alive at 10 years.

The findings presented here, from the simulation methods used to represent the described populations of patients with papillary thyroid cancer, have been observed since 1985, when Alvan Feinstein, proposed the name of Will Rogers phenomenon to describe the migration of stage seen in patients with lung cancer. In his original work, he described the changes observed in the apparent survival rates of the staging groups of patients with lung cancer due to the improvement in the sensitivity of the diagnostic tools, which allowed evidence of previously unrecognized lymph node tumor involvement, and therefore there was a migration of patients between different staging groups. In this study, it was demonstrated how the increase in the proportion of patients with lymph node positivity over time, accompanied by a constant T-stage distribution, produces an apparent but false improvement in the specific prognosis of each staging group, while the individual and the total patient population prognosis does not change [12].

After Feinstein's findings, multiple studies in oncology have shown that new imaging tools allow the detection of cancer metastases before they are clinically evident, as a consequence, more patients will be classified into more advanced stages of metastatic disease from a stage of less severity, such stage migration results in an apparent improvement in the survival of patients in both staging groups and has been demonstrated in multiple pathologies, such as lung, prostate, breast and anal cancer [8-12]. This epidemiological paradox has even been demonstrated in non-oncological settings, such as multiple sclerosis [7].

In this way, using tools and simulation models, we achieved an approach to determining the impact of the phenomenon of lymph node migration on the survival of patients with papillary thyroid cancer undergoing prophylactic lymph node dissection, and how the improvement in outcomes documented in several meta-analyzes it can be attributed to a stage migration phenomenon.

Compliance with ethical standards

Informed consent: This study is a review of the literature, and as such, there is no need for informed consent. The Institutional Ethics Committee approved the design and methodology of the study.

Conflict of interest: None declared by the authors.

Funding source: funded by the authors.

Authors' contribution:

- Conception and design of the study: José Eduardo Agamez-Fuentes, Álvaro Enrique Sanabria.
- Data acquisition: José Eduardo Agamez-Fuentes, Álvaro Enrique Sanabria.
- Data analysis and interpretation: José Eduardo Agamez-Fuentes, Álvaro Enrique Sanabria.
- Drafting the manuscript: José Eduardo Agamez-Fuentes, Álvaro Enrique Sanabria.
- Critical review: José Eduardo Agamez-Fuentes, Álvaro Enrique Sanabria.

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Annex 1. PubMed search strategy.

"thyroid"[All Fields] AND ("cancer"[All Fields] OR "carcinoma"[All Fields]) AND "papillary"[All Fields] AND "prophylactic"[All Fields] AND central[All Fields] AND "neck"[All Fields] AND "dissection"[All Fields] AND ("2010/04/18"[PDat] : "2020/04/14"[PDat])

Annex 2. Output of the simulations for the cN0 population and micrometastases.

clear

** We will simulate a population of 1,000,000 patients:

set obs 100000

** We fix the seed:

set seed 2345

** Risk of death or outcome to be studied of the dichotomous state "b" of the variable studied: for example, aca rdb may be the risk of death of patients with negative nodules:

scalar rdb=0.15

** Risk of death or outcome that you want to study from the dichotomous state "a", which is the complementary one in the dichotomous outcome "b", for example here would be the risk of death of patients with positive nodules:

scalar rda=0.65

** Now we define the prevalence of state "a", for example, a prevalence of 25% of positive nodules is defined below:

scalar pa=0.25

** Now we define the n=1 for the binomial distribution, thus converting it into a bernoulli:

generate n=1

** Next we define the probability mass function (bernoulli distribution) of the state "a" of the variable to be studied, for example lymph node involvement:

generate a=rbinomial(n, pa)

** We tabulate the probability mass function to see the events:

tab a

** We generate the probability mass function of the outcome to be studied for the population according to the states of the variable, in this case deaths:

generate m=(1-a)*rbinomial(n,rdb)+a*rbinomial(n,rda)