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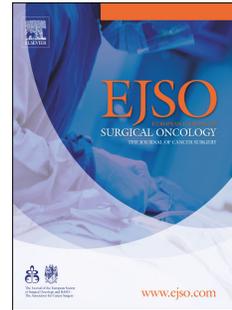
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# Age Disparities in Referrals to Specialist Surgical Care for Papillary Thyroid Cancer

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**Abstract**

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*Aims:* Referrals to specialist surgical care for papillary thyroid cancer are significantly influenced by patient age and the presence of lymph node metastases. This study sought to clarify whether younger patients with papillary thyroid cancer are referred more often because of their more frequent and more numerous lymph node metastases or because of age alone.

*Methods:* Analysis of 832 consecutive patients with papillary thyroid cancer referred to a tertiary surgical center in Germany between 1994 and 2009.

*Results:* Age (especially when categorized at 30 years) and lymph node metastases were independently associated with referral distance. Younger age was consistently correlated with greater referral distance. The effect of age was stronger in node-negative patients referred for initial operations and weaker in node-positive patients referred for reoperations. Conversely, lymph node metastases were associated with greater travelling distance, more in older than younger patients referred for reoperations, but did not seem to play any role in referrals for initial operations.

*Conclusions:* Despite their better prognosis, younger patients with papillary thyroid cancer were referred to specialist care across significantly greater distances, regardless of their lymph node status, than older patients who have a worse prognosis. The causes underlying these age disparities in referrals to specialist care warrant further research.

**Introduction**

(Word Count: 2617)

For many, usually more sophisticated interventions, distance to a referral center is an important determinant of how intensively specialist resources are utilized. Semi-quantitative research indicated the existence of a two-way referral bias in patients with lymphoma residing near a specialist center or at a distance<sup>1</sup> and patients with papillary thyroid cancer living in postal code regions clustered according to distance:<sup>2</sup> the greater the distance the more advanced the disease and the younger the patient.

From a public health perspective, discrimination by extent of disease is desirable in deciding whom to refer for specialist care, concentrating health care resources on those patients believed to be in greatest need of them. Conversely, the presence of age disparities in referrals for a given condition may arouse concern because of the suggestion that a certain group of patients, such as the elderly, may be put at a disadvantage by withholding care they depend on. Indeed, patients with differentiated thyroid cancer aged more than 60 years suffer higher rates of locoregional and distant recurrence and have a bleaker prognosis than younger adults.<sup>3</sup> Conversely, children and adolescents with papillary thyroid cancer reveal more often node-positive tumors with more positive nodes than adults. In these patients, conceivably, young age may simply reflect the presence of more positive nodes or more extensive disease.

Statutory and private health insurance in Germany cover physician and hospital fees for all recognized surgical and medical treatments nationwide, with no geographic limitations attached. Still, traveling costs may not always be covered in full, and sometimes are not refunded at all. Under these seemingly quasi-ideal conditions, non-

monetary factors, such as extent of disease, should drive decisions to refer patients for specialist care. In order not to lose information, quantitative analyses of factors relevant to decisions to refer for specialist surgical care should be based on absolute, rather than categorized, distance between two sites.

A systematic review of the pertinent literature suggests that such quantitative analyses have not yet been conducted. The current investigation aimed to quantify the independent contributions of age and lymph node metastases in referrals to a specialist surgical center for papillary thyroid cancer.

## **Patients and Methods**

### *Study Population*

A total of 832 consecutive patients with papillary thyroid cancer were referred between November 1994 and March 2009 to this institution. Initial operations were performed on 291 patients who revealed tumors with a mean tumor size of 14 mm, 41% of which were node-positive. Reoperations were carried out on 541 patients who displayed tumors with a mean tumor size of 24 mm, 53% of which were node-positive. The study population encompassed 653 patients with papillary thyroid cancer previously included in a semi-quantitative analysis of factors influencing referral patterns in papillary, follicular and medullary thyroid cancer.<sup>2</sup> For papillary thyroid cancer, this study consistently identified age and presence of lymph node metastases as the sole factors consistently varying

with distance to the referral center, without assessing their independent impacts on referral distance.

#### *Extent of Dissection*

Total thyroidectomy was or had been carried out in 779 patients (94%), and less extensive thyroid resection in 53 patients (6%). Of the 832 patients, 669 patients (80%) underwent systematic dissection of the central cervical lymph node compartment, as described elsewhere.<sup>4</sup> The lateral cervical compartments were dissected in 323 (39%; ipsilateral) and 117 patients (14%; contralateral), and the mediastinal compartment in 36 patients (4%), respectively. At least one of the four lymph node compartments of the neck and mediastinum was or had been dissected in 702 patients (84%) of the study population. All clinical interventions represented standard practice of care and agreed with the practice guidelines of the German Society of Surgery.<sup>5</sup> Before surgery, informed consent was obtained from the patients or their legal guardians for each procedure in accord with the ethical standards of the Helsinki Declaration of 1975.

#### *Histopathologic Examination and Staging*

All specimens were subjected to histopathologic examination. A diagnosis of lymph node metastasis always required histopathologic confirmation. Lymph node yield, i.e. the ratio of positive to removed nodes, from both initial operations and from reoperations was calculated based on those nodes dissected at this institution, discounting all nodes excised elsewhere. The thyroid halves were sectioned horizontally from the superior to the inferior pole, as described previously.<sup>6</sup> After fixation in formalin, the whole thyroid gland was embedded in paraffin. Soft tissue and lymph nodes were processed

separately. Conventional staining (hematoxylin and eosin) and, where appropriate, thyroglobulin immunohistochemistry was performed on every surgical specimen, using the standard avidin-biotin complex peroxidase approach. Papillary thyroid cancers were diagnosed according to the World Health Organization histologic classification of tumours.<sup>7</sup>

#### *Location of, and Distance to, the Specialist Surgical Center*

The Department of General, Visceral, and Vascular Surgery is located in Halle (Saale), a city with a population of 230,000. Because of its geographic location, the Department can receive referrals from all four cardinal points from a distance of 200 kilometers (125 miles); and from 3 cardinal points from a distance of 400 kilometers (250 miles). The maximum distance - for referrals from South-Western Germany - was 530 kilometers (330 miles). For the purpose of the study, referrals from abroad were disregarded. The distance from the patient's place of residence to the referral center (Halle) was measured with the use of an internet-based inter-city distance calculator accessible for free at <http://www.postleitzahl.org/entfernung.html> and rounded to the nearest kilometer. The calculator algorithm approximates the linear distance between two cities, the points of reference being the city centers. For Halle residents referred within the city of Halle, the calculator algorithm accordingly sets inter-city distance to zero. Nearest distance from a residence outside Halle to the specialist surgical center in Halle was 10 kilometers (6 miles). Altogether, 346 patients (42%) were referred from within a perimeter of up to 100 km (60 miles); 196 patients (24%) from between 101 km (60 miles) and 200 km (125 miles); 112 patients (13%) from between 201 km (125 miles)

and 300 km (190 miles); 140 patients (17%) from between 301 km (190 miles) and 400 km (250 miles); and 38 patients (4%) from more than 400 km (250 miles) away.

### *Statistical Analysis*

Categorical and continuous data were tested on univariate analysis using the two-tailed Fisher's exact test and one-way analysis of variance (ANOVA), respectively. Spearman rank correlation coefficient ( $\rho$ ) was calculated to assess correlations between categorical and metric variables. The level of statistical significance (all values were two-tailed) was set at  $< 0.05$ .

## **Results**

### *Referral Distance by Patient Age and Operative Setting*

An inverse relationship was found between patient age (grouped in 10-year bands) and referral distance (Tab. 1): With increasing age, mean distance to the specialist center declined for initial operations by 300% (from 327 to 109 km;  $P < 0.001$ ;  $r = -0.33$ ), and for reoperations by 50% (from 228 to 148 km;  $P < 0.001$ ;  $r = -0.17$ ). When patient age was categorized at 30 years, mean referral distance fell for initial operations by 100% (from 212 to 108 km;  $P < 0.001$ ) and for reoperations by 50% (from 237 to 163 km;  $P < 0.001$ ). In general, patients travelled more than 30% farther for reoperations than for initial operations (means of 179 vs. 133 km;  $P < 0.001$ ).

### *Referral Distance by Number of Positive Nodes and Operative Setting*

A direct relationship, stronger for reoperations than for initial operations, was identified between an increasing number of positive nodes (grouped in bands of 0, 1-5, 6-10, and >10 nodes) and referral distance (Tab. 2): With more positive nodes, mean referral distance prolonged for reoperations by 70% (from 136 to 235 km;  $P < 0.001$ ;  $r = 0.34$ ), but for initial operations only by 50% (from 123 to 190 km;  $P = 0.06$ ;  $r = 0.18$ ). When node-positive patients were compared with node-negative patients, mean referral distance extended for reoperations by 70% (from 136 to 227 km;  $P < 0.001$ ) and for initial operations by 40% (from 123 to 167 km;  $P = 0.025$ ). Altogether, patients were referred across greater distances for reoperations than for initial operations (means of 180 vs. 152 km;  $P = 0.010$ ).

There was a significant correlation between the number of positive nodes grouped in bands of 0, 1-5, 6-10, and >10 nodes and the number of nodes removed at both the initial operation ( $r = 0.62$ ;  $P < 0.001$ ) and at reoperation ( $r = 0.58$ ;  $P < 0.001$ ).

### *Referral Distance by Patient Age, Number of Positive Nodes and Operative Setting*

Depending on the operative setting, the impact of age (grouped in 10-year bands) and positive nodes (grouped in bands of 0, 1-5, 6-10, and >10 positive nodes) on referral distance varied significantly (Tab. 3):

Patients aged 30 years and younger travelled for initial operations twice as far (means of 214 vs. 104 km;  $P = 0.002$ ) than older patients when node-negative, and 70% farther (means of 219 vs. 128 km;  $P < 0.001$ ) when node-positive. For reoperations, these incremental rates were more than halved: Patients aged 30 years and younger travelled only 40% longer distances than older patients (means of 180 vs. 130 km;  $P = 0.023$ )

when node-negative, and only 20% longer distances (means of 259 vs. 211 km;  $P = 0.005$ ) when node-positive.

With more positive nodes, mean referral distance for reoperations was 65% greater in patients older than 30 years (214 versus 130 km;  $P < 0.001$ ;  $r = 0.30$ ), and 40% greater in patients aged 30 years or younger (257 versus 180 km;  $P = 0.009$ ;  $r = 0.25$ ). For reoperations, node-positive patients travelled 60% farther (means of 211 vs. 130 km;  $P = 0.001$ ) than their node-negative peers when older than 30 years; and 40% farther (means of 259 vs. 180 km;  $P = 0.002$ ) when younger than 30 years. For initial operations, the number of positive nodes had no significant effect on referral distance in either age group.

#### *Time Trends in Referral Patterns to the Specialist Surgical Center*

When patient age (categorized at 30 years) and lymph node status were stratified by referral period (1994-1999, 2000-2004, and 2005-2009; Tab. 4), no significant time trends emerged other than a time-dependent increase in mean referral distance among node-negative patients referred for reoperations: for older patients by 170% (from 69 to 189 km;  $P < 0.001$ ;  $r = 0.44$ ); and for younger patients by 280% (from 48 to 184 km;  $P = 0.047$ ).

## **Discussion**

In the present study, patient age (in particular when categorized at age 30 years) and lymph node metastases were independently associated with referral distance. Younger

age was consistently associated with greater referral distance, having the strongest effect in node-negative patients referred for initial operations and the weakest effect in node-positive patients referred for reoperations. Lymph node metastases, conversely, were associated with greater travelling distance more in older than younger patients referred for reoperations, without playing any significant role in referrals for initial operations. Overall, these effects were fairly robust and largely independent of time. Yet they varied somewhat in magnitude according to the operative setting. Healthcare Cost and Utilization Project National Inpatient Sample data from the US Agency for Healthcare Research and Quality suggest that there are significant outcome disparities among younger children undergoing thyroidectomy and parathyroidectomy<sup>8</sup> with regard to injury to the recurrent laryngeal nerve (3.8%, 1.1%, and 0.6% in children aged 0-6 yr, 7-12 yr and 13-18 yr, respectively;  $P < 0.01$ ). Awareness of this association would, at least partially, explain the age-related referral pattern seen in the present study. The time-dependent increase in travelling distance among - eventually node-negative - patients referred for reoperations perhaps may reflect the recent trend of dedicated centers to make more use of routine central lymph node dissection for papillary thyroid cancer in keeping with the recent management guidelines of the American<sup>9</sup> and European Thyroid Association.<sup>10</sup>

#### *Strengths and Limitations of the Current Study*

The current study is noteworthy for the high degree of systematic lymph node dissection for papillary thyroid cancer, enabling accurate determination of lymph node metastases. As a consequence, the potential for misclassification of lymph node status, which would have rendered the node groups under comparison more alike, is likely to be smaller than

in other studies on papillary thyroid cancer. Causes underlying decisions not to refer patients to our institution could not be ascertained because these patients remain unknown for obvious reasons. It was also not clear who made the decisions to refer, or not to refer, or whether this was a joint decision of more than one party: (i) older patients unwilling to travel long-distance for professional or familial reasons; (ii) physicians believing that older patients fared equally well with operations at community hospitals because of the longevity enjoyed by many patients with papillary thyroid cancer; (iii) third party payers steering older adults towards local hospitals for convenience or economic reasons, or (iv) any combination of the above. Inability to travel long-distance did not seem to have affected decisions regarding referrals because papillary thyroid cancers, unlike other conditions,<sup>11</sup> rarely compromise general health unless they are very advanced and widely metastatic. In addition, many adult patients were still in their thirties, forties, fifties, or sixties and had no major co-morbidity. Socioeconomic variables were not measured in this study. Nevertheless, the patients' economic resources, in all likelihood, did not drive decisions regarding referrals since older adults, who travelled significantly shorter distances to our institution, usually are more affluent than children, adolescents, or young adults. Unlike patient age, the extent of disease is less likely, if at all, to influence decisions regarding referrals for specialist care in conditions that are disclosed by sensitive biomarkers and for which there are no effective therapies other than surgery, such as medullary thyroid cancer.<sup>2</sup> In papillary thyroid cancer, the interference of thyroid-stimulating hormone (TSH) and anti-thyroglobulin antibodies with thyroglobulin serum concentrations can diminish the relevance of thyroglobulin as a tumor marker.<sup>12</sup>

### *Clinical Implications*

The relative increments in referral distance for patients with papillary thyroid cancer are likely to extend to other health care systems providing a high level of social-security protection where patients and physicians can make individual decisions to seek national specialist care regardless of travel distance within that country. They may apply less to health care systems where individual decisions to travel for specialist care are largely predicated upon insurance company agreements or government regulations restricting referrals outside the community setting.

Although the German health care system enables out-of-area referrals for specialist care, the current data suggest room for improvement with regard to older patients with papillary thyroid cancer, whose prognosis tends to be bleaker than those of younger patients. In keeping, a recent US study found that adults with differentiated thyroid cancer are unlikely to receive systematic lymph node dissections during the initial operation at non-specialist institutions, even when they have node-positive papillary thyroid cancers.<sup>13</sup> This may be due to (i) the need for greater surgical skills because of the incremental surgical morbidity attendant to lymph node dissection in the neck,<sup>14, 15</sup> (ii) overestimation of the ability of radioiodine therapy to ablate residual disease, or (iii) the perceived indolent course of the disease, rendering dissection of nodes not worthwhile. Patients who underwent exclusively thyroid resections may ultimately require reoperations in the neck for disease not cleared at the initial operation. Reoperations in the neck, coming at a substantial cost to the health care system, can be traumatic to patients because of the associated excess surgical morbidity. If patients received adequate initial operations straight away or were referred immediately for

specialist surgical care, as many as 82% of reoperations for persistent, and 25% of reoperations for recurrent papillary thyroid cancer may be preventable.<sup>13</sup>

More research is needed to explore the pervasiveness of and underlying causes for these – seemingly paradox - age disparities in referrals for specialist care before targeted intervention strategies can be devised.

**Conflict of interest**

The authors state that they have no conflict of interest.

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**Tab. 1: Referral Distance by Patient Age and Operative Setting**

Age, yr	Initial neck surgery			Cervical reoperation			$P^{\ddagger}$
	Patients, n	Distance, km mean [95% CI]	$P^{\dagger}$	Patients, n	Distance, km mean [95% CI]	$P^{\dagger}$	
0-10	3	327 [291 ; 363]		4	228 [79 ; 377]		0.14
11-20	36	220 [176 ; 264]		40	242 [198 ; 286]		0.48
21-30	30	191 [144 ; 238]		74	234 [204 ; 264]		0.12
31-40	46	133 [100 ; 166]		95	194 [168 ; 221]		0.007
41-50	52	122 [87 ; 158]		82	164 [136 ; 191]		0.07
51-60	53	88 [59 ; 116]		103	127 [103 ; 150]		0.047
61-70	46	91 [62 ; 120]		98	178 [150 ; 205]		< 0.001
> 70	25	109 [68 ; 150]	< 0.001 <sup>a</sup>	45	148 [111 ; 186]	< 0.001 <sup>b</sup>	0.18
≤ 30	69	212 [181 ; 243]		118	237 [213 ; 260]		0.21
> 30	222	108 [94 ; 123]	< 0.001	423	163 [151 ; 176]	< 0.001	< 0.001
Total	291	133 [119 ; 147]		541	179 [168 ; 190]		< 0.001

CI, confidence interval

†: Across all age groups within one operative setting.

‡: Initial neck surgery versus cervical reoperation within one age group.

a:  $r = -0.33$ ,  $P < 0.001$ ; Spearman rank correlation coefficient ( $\rho$ ).

b:  $r = -0.17$ ,  $P < 0.001$ ; Spearman rank correlation coefficient ( $\rho$ ).

**Tab. 2: Referral Distance by Number of Positive Nodes and Operative Setting**

Positive nodes, n	Initial neck surgery			Cervical reoperation			
	Patients, n	Distance, km mean [95% CI]	$P^{\dagger}$	Patients, n	Distance, km mean [95% CI]	$P^{\dagger}$	$P^{\ddagger}$
0	64	123 [95 ; 151]		268	136 [122 ; 151]		0.44
1-5	53	158 [122 ; 195]		149	215 [194 ; 236]		0.008
6-10	22	144 [84 ; 205]		54	254 [219 ; 289]		0.001
> 10	42	190 [150 ; 230]	0.06 <sup>a</sup>	50	235 [199 ; 271]	< 0.001 <sup>b</sup>	0.09
0	64	123 [95 ; 151]		268	136 [122 ; 151]		0.44
≥ 1	117	167 [143 ; 191]	0.025	253	227 [211 ; 243]	< 0.001	< 0.001
Total	181	152 [133 ; 170]		521	180 [169 ; 192]		0.010

CI, confidence interval

Excluding 130 patients without systematic neck dissection.

†: Across all node groups within one operative setting.

‡: Initial neck surgery versus cervical reoperation within one node group.

a:  $r = 0.18$ ,  $P = 0.018$ ; Spearman rank correlation coefficient ( $\rho$ ).

b:  $r = 0.34$ ,  $P < 0.001$ ; Spearman rank correlation coefficient ( $\rho$ ).

**Tab. 3: Referral Distance by Patient Age, Number of Positive Nodes and Operative Setting**

Setting	Positive nodes, n	≤ 30 yrs of age			> 30 yrs of age			$P^{\ddagger}$
		Patients, n	Distance, km mean [95% CI]	$P^{\ddagger}$	Patients, n	Distance, km mean [95% CI]	$P^{\ddagger}$	
Initial surgery	0	11	214 [112 ; 316]		53	104 [79 ; 130]		0.002
	1-5	16	215 [160 ; 270]		37	134 [89 ; 179]		0.038
	6-10	9	219 [114 ; 325]		13	92 [24 ; 160]		0.028
	> 10	25	221 [168 ; 275]	0.99 <sup>a</sup>	17	144 [86 ; 201]	0.38 <sup>a</sup>	0.05
	0	11	214 [112 ; 316]		53	104 [79 ; 130]		0.002
	≥ 1	50	219 [184 ; 253]	0.91	67	128 [98 ; 159]	0.25	< 0.001
Reoperation	0	34	180 [132 ; 229]		234	130 [115 ; 145]		0.023
	1-5	43	245 [207 ; 283]		106	203 [177 ; 228]		0.07
	6-10	16	303 [256 ; 350]		38	234 [189 ; 279]		0.07
	> 10	25	257 [203 ; 310]	0.009 <sup>b</sup>	25	214 [163 ; 265]	< 0.001 <sup>c</sup>	0.24
	0	34	180 [132 ; 229]		234	130 [115 ; 145]		0.023
	≥ 1	84	259 [233 ; 286]	0.002	169	211 [191 ; 231]	< 0.001	0.005

CI, confidence interval

Excluding 130 patients without systematic neck dissection.

†: Across all node groups within one age group and operative setting.

‡: ≤ 30 yrs. of age versus > 30 yrs. of age within one node group and operative setting.

a: No Spearman rank correlation coefficient ( $\rho$ ) given as not significant.

b:  $r = 0.25$ ,  $P = 0.007$ ; Spearman rank correlation coefficient ( $\rho$ ).

c:  $r = 0.30$ ,  $P < 0.001$ ; Spearman rank correlation coefficient ( $\rho$ ).

**Tab. 4: Time Trends in Referrals to the Specialist Surgical Center**

Operative setting	Patient age	Positive nodes, n	Patients, n	Referral period			P
				1994-1999 (n = 157)	2000-2004 (n = 264)	2005-2009 (n = 281)	
Initial surgery	≤ 30 yrs	0	11	145 [0 ; 420]	359 [181 ; 537]	211 [38 ; 384]	0.29
		≥ 1	50	162 [0 ; 410]	243 [189 ; 297]	205 [154 ; 255]	0.40
	> 30 yrs	0	53	55 [25 ; 85]	118 [65 ; 171]	127 [87 ; 166]	0.06
		≥ 1	67	118 [52 ; 184]	101 [59 ; 143]	153 [100 ; 205]	0.34
Reoperations	≤ 30 yrs	0	34	48 [0 ; 102]	223 [146 ; 300]	184 [105 ; 263]	0.047
		≥ 1	84	252 [190 ; 314]	274 [236 ; 313]	249 [204 ; 295]	0.67
	> 30 yrs	0	234	69 [46 ; 92]	124 [102 ; 146]	189 [161 ; 217]	< 0.001 <sup>a</sup>
		≥ 1	169	172 [121 ; 222]	215 [179 ; 251]	224 [197 ; 252]	0.17
Total	any	any	702	119 [99 ; 139]	177 [161 ; 193]	199 [184 ; 214]	< 0.001 <sup>b</sup>

CI, confidence interval

Excluding 130 patients without systematic neck dissection.

a:  $r = 0.44$ ,  $P < 0.001$ ; Spearman rank correlation coefficient ( $\rho$ ).

b:  $r = 0.24$ ,  $P < 0.001$ ; Spearman rank correlation coefficient ( $\rho$ ).