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Indeterminate nodules by the Bethesda system for reporting thyroid cytopathology in Israel: Frequency, and risk of malignancy after reclassification of follicular thyroid neoplasm with papillary-like features



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ABSTRACT

Objective: We aimed to determine the frequency and risk of malignancy (ROM) for indeterminate thyroid nodules, categories III (B3) and IV (B4) of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC), at a large institution in Israel. Additionally, we investigated the impact of redefining follicular neoplasm with papillary-like nuclear features (NIFTP) as non-malignant on malignancy rates.

Methods: In this retrospective study of all thyroid fine needle aspirations (FNAs) performed at Tel Aviv-Sourasky Medical Center between January 2013 and December 2015, we assessed ROM for B3 and B4 nodules. Potential risk factors thought to affect a-priori ROM were assessed. Suspected NIFTP lesions were re-examined, and if proven, reclassified as benign.

Results: 3701 nodules were sampled in 2919 FNAs performed on 2674 patients. B3 reports comprised 7.7% of all nodules (n = 284); B4 represented 3.6% (n = 132). In multivariate logistic regression, male gender, being of former Soviet Union origin, and smoking increased ROM for B3 nodules by a factor of 7.97 (P = 0.002; CI: 2.2–23.4), 9.15 (P = 0.021; CI: 1.4–60.0), and 11.0 (P = 0.001; CI 2.8–44.8), respectively. Reclassifying NIFTP decreased ROM from 14% to 12.5% for B3, and from 26.7% to 25% for B4 nodules. NIFTP comprised 9.5% of previously diagnosed resected malignant tumors.

Conclusions: The relative frequencies of B3 and B4 nodules and their associated malignancy rates were consistent with previous series. Risk factors identified for malignancy may help characterize patients most likely to benefit from surgery. Reclassifying NIFTP had a substantial impact on the ROM in the resected tumors previously diagnosed as malignant.

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Introduction

The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) was designed to standardize thyroid cytopathology results by classifying them into 6 categories according to risk of malignancy (ROM), thus promoting effective communication between physicians [1]. The BSRTC has been widely adopted across the world

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and is now standard for reporting thyroid cytopathology. However, during the decade since its original drafting, there have been developments such as the emergence of molecular testing [2], reclassification of follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) as non-malignant [3], and studies from different institutions documenting varying risks of malignancy (ROM) for each category. The 2017 revision of the system [4] acknowledged these advances, adapting ROM ranges particularly for indeterminate categories III-B3 (Atypia of Undetermined Significance –AUS, or Follicular Lesion of Undetermined Significance –FLUS) and IV-B4 (Follicular Neoplasm –FN, or Suspicious for a Follicular Neoplasm –SFN), to reflect the impact of including/excluding NIFTP. In addition, molecular testing has become an optional further diagnostic step in these categories.

The AUS/FLUS category encapsulates cases that cannot be easily defined as benign, suspicious, or malignant. The creators of the system viewed this category as one of last resort, initially recommending that it account for no more than 7% of all FNAs but recently acknowledging figures up to 10% [4].

Although the current publication now suggests ROM of 6–30% for category B3 and 10–40% for category B4 [4], figures depend on the nature of the series. Studies based on histopathology may overestimate malignancy risk as surgical excision is usually performed in high-risk cases, whereas studies using standard follow up may underestimate risk as some cancers may remain undiagnosed. It has been suggested that centers assess their individual ROM for indeterminate categories, to determine whether they are in accordance with prevailing statistics and identify potential reasons for divergence [5].

The BSRTC was adopted routinely at Tel Aviv Sourasky Medical Center in early 2013 after these areas of uncertainty came to light. The aims of our study were to assess Bethesda category distribution among thyroid FNA reports over a 3-year period, to re-evaluate ROM in AUS/FLUS (B3) and FN/SFN (B4) categories taking NIFTP into consideration, and to identify factors that could modify ROM.

Material and methods

Samples and data retrieving

The study was approved by the Tel Aviv Sourasky Medical Center institutional ethical committee (approval # 0663-16-TLV). A list of all ultrasound-guided FNAs performed on adult subjects (aged 18 years and above) at Tel Aviv Sourasky Medical Center from implementation of the BSRTC in January 2013 until December 2015, was generated from the computerized SNOMED (Systematized Nomenclature of Medicine) database of our pathology department. This list included subject identification and demographic details, procedure date, reporting cytopathologist (of only two), free text description of location of sampled nodules, Papanicolaou stain characteristics and nodule BSRTC category.

Files of subjects with B3 (AUS/FLUS) and B4 (FN/SFN) nodules were reviewed to retrieve relevant data such as nodule ultrasonographic characteristics, TIRADS classification [6], demographic and clinical information such as country of birth, personal and familial history of thyroid disease or malignancy, and other potential risk modifying factors such as exposure to ionizing radiation, smoking and obesity. Information pertaining to downstream procedures such as repeat FNA, molecular testing using gene expression classifier (GEC) method AFIRMA[®] (Veracyte, San Francisco, CA), and surgery was also extracted from patient charts. When surgery was performed, the computerized system was searched for histopathologic results.

FNA reports of other BSRTC categories were recorded, but no attempt was made to determine their ROM.

Specimens designated category B3 and B4 and diagnosed as encapsulated or well-circumscribed follicular variant of papillary thyroid cancer were reviewed to assess whether they fulfilled NIFTP criteria [4]. Additionally, resected tumors diagnosed as follicular variant of papillary thyroid cancer with no described features suggestive of invasion were re-assessed to determine eligibility for NIFTP category. Confirmed NIFTPs were considered non-malignant.

Statistical analysis

Demographic characteristics of subjects harboring nodules assigned to different categories were compared by variance analysis. Ratios were compared using Fisher's exact test and Pearson Chi-square test.

After classifying nodules in categories III and IV with documented follow-up as benign or malignant, subject and nodule characteristics were compared using the Student's t-test for normally distributed variables, or the Mann-Whitney test for non-parametric variables.

Potential risk factors for malignancy were analyzed first by univariate analysis, then using multivariate stepwise logistic regressions. Computations were performed using GraphPad Prism version 7.03 for Windows (GraphPad Software, La Jolla, Ca), and IBM SPSS Statistics 24 (IBM, Armonk, NY). Data are presented as mean \pm SD, and statistical significance was assumed for $P < 0.05$.

Results

Entire cohort characteristics

During the designated period, a total of 3071 nodules were aspirated in 2919 thyroid FNA procedures performed on 2674 patients (1.27 nodules/session). 2137 (80%) were women; only 537 (20%) were men. Mean age for the entire population was 56.7 ± 15.5 yrs, and women were significantly younger than men (56.0 ± 15.5 vs 59.1 ± 15.3 , $P = 0.003$).

Distribution of nodules according to BSRTC categories, and subject age and gender for various categories are shown in Table 1. Men were relatively overrepresented in nodules of higher malignant potential (categories 4 to 6) although this did not reach statistical significance, while benign B2 nodules were predominantly found in women who were younger than their male counterparts.

Outcome of B3 and B4 nodules

Follow-up was available for 128 of the 284 B3 nodules (45%). Sixty-seven (52.3%) were resected and 18 of these confirmed malignant, giving ROM of 26.9% for resected nodules. However, most B3 nodules underwent repeat aspiration and were benign, so overall ROM for B3 nodules was only 14%. Downstream steps leading to final classification are shown in Fig. 1A. Of the 132 B4 nodules, final outcome was known for 60 (45.5%). Sixteen resected nodules were malignant yielding surgical ROM of 28%, very similar to the B3 category. However, essentially all B4 nodules were resected ($57/60 = 95\%$), and overall B4 ROM was 26.7%, almost identical to surgical ROM (Fig. 1B).

The gene expression classifier (GEC) AFIRMA[®] was applied in only eleven category B3 nodules and two B4 nodules (6.9% of B3/B4 nodules). This paucity of use is explained by the fact that Israeli national health insurance does not cover this test. AFIRMA classified two B3 nodules as suspicious, both of which were benign at surgery, and 9 as benign, which were not investigated further.

Of the B4 nodules, molecular testing rendered one suspicious and the other benign. The suspicious nodule was benign at surgery,

Table 1
Relative frequency of BSRTC categories with subjects' gender and age breakdown.

Bethesda Category	Nodules N	% Total	Men/Women N/n (ratio)	Age (y) (SD)	Age Men	Age Women
B1 Non diagnostic	242	6.6	62/171 (1/2.7)	54.6 (15.2)	60.4 (14.5)	52.5 (15.0) ^b
B2 Benign	2693	72.8	379/1656 (1/4.4)	57.7 (15.0)	60.7 (13.8)	56.5 (15.3) ^b
B3 AUS/FLUS ^a	284	7.7	43/204 (1/4.7)	57.4 (14.0)	57.9 (14.6)	57.3 (13.9)
B4 Follicular or suspicious for follicular lesion	132	3.6	35/86 (1/2.5)	53.7 (15.0)	54.8 (14.0)	53.3 (15.4)
B5 Suspicious for malignancy	84	2.3	20/62 (1/3.1)	51.4 (15.7)	50.9 (18.9)	51.5 (14.8)
B6 Malignant	266	7.2	59/187 (1/3.2)	50.9 (16.7)	53.1 (20.3)	50.2 (15.4)

^a AUS: Atypia of unknown significance; FLUS: Follicular lesion of unknown significance.

^b Indicates that women were younger than men in the given category, $P < 0.001$.

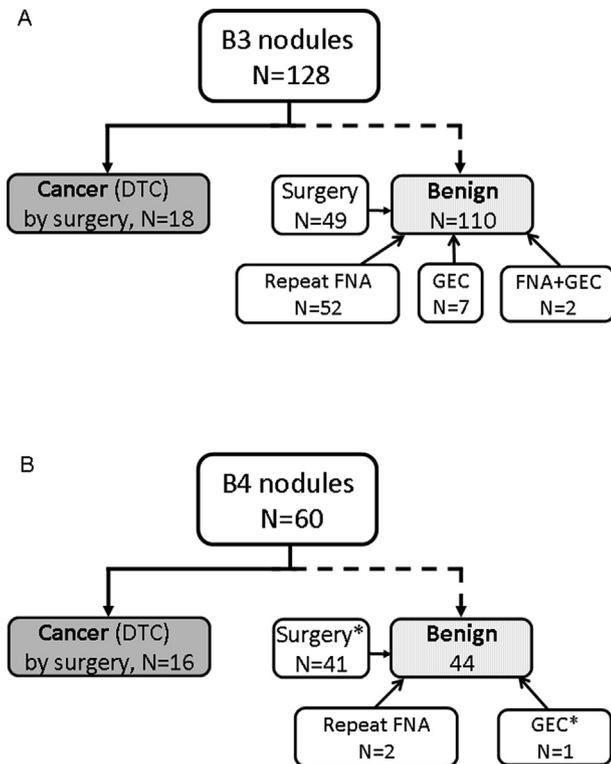


Fig. 1. Downstream procedures leading to a final diagnosis in indeterminate nodules on which information was available. A–B3 nodules. B–B4 nodules. DTC: Differentiated thyroid cancer; GEC: Gene expression classifier; * highlights the fact that one B4 nodule which returned a suspicious GEC result, was benign at surgery, one other nodule with a benign GEC report was considered as such and not referred to surgery.

and the second nodule did not undergo further investigation.

Histopathological diagnoses of surgically excised benign B3 and B4 nodules (49 and 41 respectively) consisted mainly of hyperplastic adenomatous and colloid nodules (Fig. 2). The distribution of thyroid cancer subtypes among malignant nodules was similar in both categories: malignant B3 nodules included 8 classical papillary cancers, 8 follicular variants of PTC, 1 Hürthle cell carcinoma, and 1 follicular carcinoma, while malignant B4 nodules included 5 classical papillary cancers, 6 follicular variants, 2 Hürthle cell carcinomas and 3 follicular carcinomas. Notably, all malignancies were well-differentiated thyroid cancers, and no cases of medullary cancer were identified.

Impact of NIFTP on ROM in categories III and IV after reclassification as non-malignant

The SNOMED database encompassed 231 resected tumors with histopathological diagnosis of thyroid malignancy, after excluding

incidental foci of microscopic papillary thyroid cancer. Tumors designated noninvasive encapsulated follicular variant of papillary cancer underwent review to establish whether they fulfilled criteria for NIFTP. Following revision, 22 nodules qualified as NIFTP, comprising 9.5% of “malignant” nodules. However, pre-surgical cytology was available for only 11, as the remainder were evaluated elsewhere. Of these nodules, presurgical cytopathological evaluation categorized 5 nodules as B6, one each as B1, B2, B4 and B5, and two as B3. Therefore, reclassification of NIFTP as non-malignant led to a relative reduction in overall ROM for B3 from 14% to 12.5%, and for B4 from 26.7% to 25%. Calculated for resected nodules only, this relative reduction was very similar, from 26.9% to 23.9% for B3 and from 28% to 26.3% for B4.

Factors affecting ROM in categories III and IV nodules

The goal of this analysis was to assess potential factors that may affect ROM for categories III and IV, so as to tailor management of these nodules to patient profile. To this end we evaluated demographic variables (gender, age, and country of birth, particularly the former Soviet Union), clinical factors (ionizing radiation exposure, obesity, smoking, TSH concentration, thyroid autoimmunity, prior malignancy), and familial parameters (family history of thyroid cancer). We recorded ultrasonographic characteristics such as nodule largest diameter, echogenicity, presence of microcalcifications, irregular borders, vascularity, and TIRADS grade.

We conducted a univariate analysis on continuous and categorical variables which exonerated most variables including nodule size, the sum of suspicious sonographic features, and TIRADS score. A comparison of some variables in benign and malignant B3 and B4 nodules is shown in Table 2. We then performed logistic regression, including variables felt to potentially convey increased malignancy risk on univariate analysis. This strategy was carried out for each category separately. Variables retained in the logistic model were age, gender, birth in the former Soviet Union, and current/past smoking.

For B3 nodules, the Nagelkerke R square of the model was 0.354.

Male gender was associated with an odds ratio of 7.97 for malignancy ($P = 0.002$; CI: 2.2–23.4). Birth in the former Soviet Union increased ROM by a factor of 9.15 ($P = 0.021$; CI: 1.4–60.0), while current or past smoking increased the odds of malignancy in B3 nodules by a factor of 11.0 ($P = 0.001$; CI 2.8–44.8).

Although in univariate analysis of B4 nodules there was a trend towards younger age among patients with malignant nodules ($P = 0.074$), logistic regression using the same variables for B3 nodules showed no predictive value for age.

Discussion

The initial goal of this study was to determine our cytopathologists' use of the BSRTC system, and alignment with published reports in terms of size and ROM of various categories. Additionally,

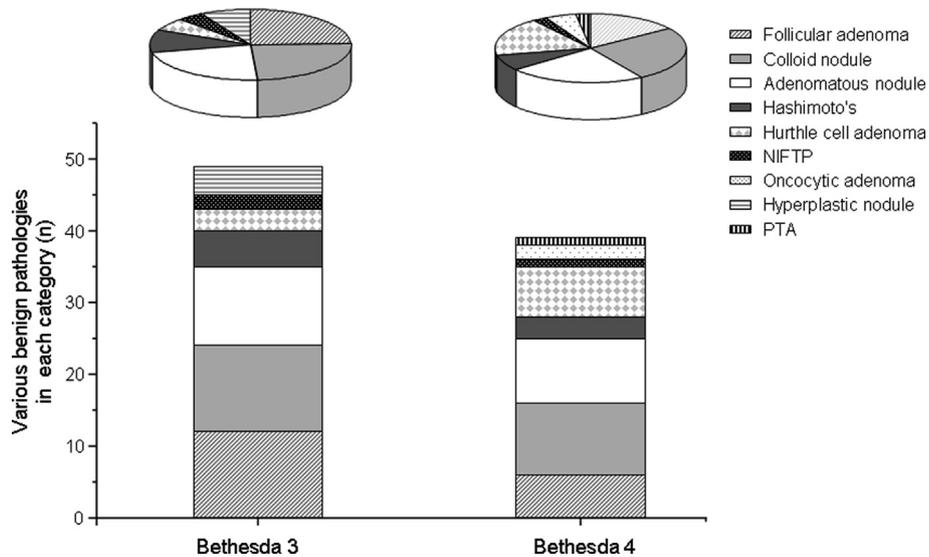


Fig. 2. Breakdown of histopathology diagnoses in benign B3 and B4 nodules. Top panel relative frequency of each diagnosis, lower panel absolute cumulative numerical distribution.

Table 2

Comparison of characteristics between benign and malignant B3 and B4 nodules. Continuous variables are given as mean (\pm SD). Significance was assessed with *t*-test or Mann-Whitney for continuous variables, or with the Fisher's exact test for categorical variables.

Category	B3		P	B4		P
	Benign N = 110	Malignant N = 18		Benign N = 44	Malignant N = 16	
Women/Men (N/n)	91/16	10/8	0.007	29/15	13/3	NS
Age (y)	58.2 (13.9)	52.4 (14.4)	0.10	56.8 (14.3)	49.1 (15.1)	0.074
Born in USSR (yes/no)	11/96	4/14	0.094	13/31	4/12	NS
Smoking (yes/no)	11/99	7/8	0.001	5/39	3/13	NS
Nodule size (mm)	23.5 (14)	17.5 (12.5)	NS	25.6 (12.9)	26.8 (11.3)	NS
Suspicious US features (n)	1.0 (0.9)	0.8 (0.7)	NS	1.7 (0.9)	1.3 (0.9)	NS

we sought to characterize our patient population, and identify demographic and clinical variables that might affect ROM for B3 and B4 nodules.

Cohort composition and Bethesda category breakdown

Although the acceptable rate of category B3 specification among thyroid cytopathology reports is up to 10% [4], rates vary significantly among series [7,8], with some reporting figures of 20–27% [9,10]. It was therefore reassuring to discover that the rate in our current series (7.7%) fit within the recommended range. In contrast, B4 nodule incidence is relatively consistent across published series, and at 3.6%, the proportion of B4 nodules in this series was fairly typical. Variations in incidence of different categories between series might stem from different practices in referral of subjects for thyroid FNA, genuine ethnic/genetic differences, and prevalence of local risk factors such as background ionizing radiation. Consequently, it was interesting to notice that the demographic composition and categorical breakdown of cytology reports in this series were consistent with a report from another Israeli institution [11], although in their study B6 malignant nodules were less frequent (2.6% vs 7.2%). Moreover, our data are in agreement with a series from Memorial Sloan Kettering Cancer Center [12] more than twice the size of ours, suggesting that ethnical differences may not play a major role in determining distribution of nodules into various categories.

ROM in B3 and B4 nodules and the impact of NIFTP

As previously noted by others [10,11], less than complete follow-up information is an inherent limitation of this type of study. Although essential to determine precise ROM, this hurdle was almost unavoidable in our study, as follow-up information was gathered from our institution's computerized records and data are missing for patients who underwent surgery or other procedures elsewhere. Ultimately, definitive diagnosis was available for almost 50% of B3 and B4 nodules. However, overall ROM for B3 nodules was 14%, similar to that found in an earlier Israeli series [11] and well in line with published literature [13–16] and figures cited by the BSRTC developers [4]. It should, however, be noted that the wide range of ROM cited for this category stems from inclusion of both surgical histopathology-based series and clinical series like ours, in which not all nodules were excised. Furthermore, some publications express figures per patient, and others per nodule, while others switch from one to the other. As the goal is to limit unnecessary surgical procedures in this category which consists mostly of benign nodules, we believe that calculating ROM using all known outcomes, and not histopathology alone, is a reasonable approach.

As regards B4 nodules, our series is essentially a surgical one, with overall ROM of 26.7% almost identical to that of resected nodules, and well within the range of previously reported malignancy rates for this category [13–16].

Another issue we sought to comprehend was the impact of reclassifying NIFTP as non-malignant on ROM for B3 and B4

nodules. It has been proposed that this category could represent up to 18.6% of all cases of papillary thyroid cancer [3], and that reclassification could dramatically alter ROM for indeterminate nodules, particularly for categories III–IV, potentially even reducing it by half. This could have a major impact on the epidemiology of thyroid cancer worldwide, and substantially alter treatment approach [17,18]. However, data from Asia seem to portray a different picture, with NIFTP reported rates an order of magnitude lower than that in the West. Indeed, in a large series encompassing 26,604 cases of PTC, only 0.8% were defined as NIFTP [19]. In a subsequent nested study focusing solely on specimens with a BSRTC cytological diagnosis and surgical follow-up, NIFTP accounted for 5.3% of reported malignancies, leading to a marginal absolute reduction in ROM [20]. In our sample, NIFTP histopathology accounted for 9.5% of all malignant nodules, a number about midway between US/European and Asian figures, and within the range of a recent collaborative US-Italian report [21]. Therefore, albeit limited by small numbers, the impact of reclassifying NIFTP as non-malignant at our institution was substantial. The impact of NIFTP reclassification on malignancy rate for B3 and B4 nodules in our study was more modest, but was probably underestimated due to small sample size, low availability of preoperative cytology for NIFTP nodules (11/22) and low resection rates for B3 nodules (52.3%). Larger studies are needed to accurately assess the effect of NIFTP reclassification on malignancy rate for nodules of various Bethesda categories.

Factors affecting ROM

As most nodules in indeterminate categories B3/B4 are benign, and as molecular markers are not widely available in Israel, we were interested to establish whether socio-demographic, lifestyle, and sonographic features could predict malignancy and help triage subjects most likely to benefit from surgery. The only 3 factors that significantly impacted ROM in B3 nodules were male gender, immigration to Israel from the former Soviet Union, and current/former smoking. Age was not a distinguishing factor, nor were “suspicious sonographic features” such as microcalcifications, hypoechogenicity and nodule size. In contrast for B4 nodules, possibly because of the smaller number of nodules assessed, no risk factor for malignancy emerged. Similar attempts at stratifying a-priori risk of malignancy in B3 nodules have been conducted in previous series with conflicting results. In the 2014 study from Memorial Sloan Kettering Cancer Center, younger age, larger size and hypervascularity were risk factors for malignancy in univariate but not in multivariate analysis [12]. Authors of a comparable cohort from Turkey came to similar conclusions, but the factors held in multivariate logistic regression [22]. In contrast, in a more recent series consisting of excised nodules only, all these factors, including size, had no predictive power [23]. Likewise, neither ATA ultrasound characteristics, nor TIRADS score added predictive value in nodules with indeterminate cytology [24,25]. We had anticipated immigration from the former Soviet Union to be a risk factor for malignancy, as exposure to Chernobyl fallout has been associated with increased incidence of thyroid cancer even 30 years after the accident [26].

Smoking, either current or past, was the most powerful risk modifier, increasing ROM in B3 nodules 11-fold. We have no immediate explanation for this finding, which came as a surprise as prior literature ascribed a protective role for smoking against thyroid cancer [27].

From our analysis we would therefore suggest that in Israel, earlier triage to surgery be offered to a male patient with B3 cytology on thyroid aspiration, particularly if this person emigrated from the former Soviet Union and has a history of smoking. These

high-risk features may be specific to our population.

Strengths and limitations

The major strength of this study is that only two cytopathologists were responsible for the 3071 cytopathology reports. This limited the inter-observer variability widely documented in thyroid cytopathology reading, even after implementation of the BSRTC whose purpose was to standardize this field. In addition, the relatively late implementation of the BSRTC at our institution allowed awareness by our pathologists of potential pitfalls. The similarity of our cohort composition in demographic details and Bethesda category breakdown with a similar-size Israeli series [11] suggests that our findings are generalizable to the Israeli population. Moreover, assessment of multiple potential risk factors in this series enables profiling of subjects with B3 nodules in our country who should preferentially be triaged to surgery.

Our study's major limitation lies in the incomplete follow-up of approximately half of indeterminate nodules. Although this series allows a first appraisal of NIFTP frequency among surgical specimens in Israel and its impact on ROM, this assessment is affected by the same limitation, as pre-surgical cytological reports were available for only half our cases.

In conclusion, in a large series of thyroid nodules aspirated at one Israeli institution, BSRTC category B3/B4 report rates and ROM were in accordance with previous local and international reports. Due to infrequent use, GEC procedures were of limited assistance in ruling out malignancy. We report for the first time the relative frequency of NIFTPs among malignant surgical samples in Israel, and show that reclassification of this entity as benign had a noteworthy impact on ROM. Additionally, factors including male gender, immigration from the former Soviet Union, and smoking increased malignancy risk for B3 nodules, potentially enabling us to identify subjects who may benefit from early surgery in this country.

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Conflict of interest

The authors report no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this chapter can be found online at <https://doi.org/10.1016/j.ejso.2019.03.015>.

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