Guidelines on the management of cystic renal lesions

Patrick O. Richard\textsuperscript{1}, Philippe D. Violette\textsuperscript{2}, Michael A.S. Jewett\textsuperscript{3}, Frederic Pouliot\textsuperscript{4}, Michael Leveridge\textsuperscript{5}, Alan So\textsuperscript{6}, Tom F. Whelan\textsuperscript{7}, Ricardo Rendon\textsuperscript{8}, Antonio Finelli\textsuperscript{3}

\textsuperscript{1}Division of Urology, Department of Surgery, Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC
\textsuperscript{2}Division of Urology, Woodstock General Hospital, Woodstock, ON
\textsuperscript{3}Division of Urology, Departments of Surgery and Surgical Oncology, Princess Margaret Cancer Centre, University Health Network and the University of Toronto, Toronto, ON
\textsuperscript{4}Division of Urology, Department of Surgery, Université Laval, Centre de Recherche du Centre Hospitalier Universitaire de Québec, Québec, QC
\textsuperscript{5}Department of Urology, Queen’s University, Kingston General Hospital, Kingston, ON
\textsuperscript{6}Division of Urology, Department of Surgery, University of British Columbia, Vancouver, BC
\textsuperscript{7}Division of Urology, Department of Surgery, Saint John Regional Hospital, Dalhousie University, Saint John, NB
\textsuperscript{8}Department of Urology, QEII Health Sciences Centre, Dalhousie University, Halifax, NS

Please address all correspondence to:
Patrick Richard, MD, FRCSC, MSc, Division of Urology, Department of Surgery, Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, 3001-12ieme avenue Nord, Sherbrooke, Qc, Canada, J1H 5N4, patrick.richard@usherbrooke.ca

Keywords: Bosniak, Nephrectomy, Renal cell carcinoma, Renal cysts

Word count: 3195

Total number of tables: 2

Total number of manuscript pages: 21

Source of funding: The authors have no other competing interests to disclose
Guidelines on the management of cystic renal lesions – Richard et al

Tribute:

These guidelines are largely based on the work of a giant in the field of uro-radiology, Dr. Morton A. Bosniak, who recently passed away on September 7th, 2016. Dr. Bosniak was a pioneer in the field of renal mass evaluation. His work significantly impacted the management of both solid and cystic kidney masses. Dr. Bosniak was the first to recognize the need for structured categorization of cystic renal masses and his seminal classification of the malignant potential of cystic renal masses remains his signature work. The Bosniak classification is applied worldwide and is known to every urologist and radiologist as well as to any clinicians who care for patients with renal disease. As a commemoration of his life and work, the authors would like to dedicate these guidelines to his memory.
1.0 Introduction

Cystic renal lesions are usually diagnosed incidentally on routine imaging. With the increased use of abdominal imaging, there is a growing number of individuals being diagnosed with renal cystic disease. (1) It is estimated that up to one third of individuals over 60 years of age will be diagnosed with at least one simple renal cyst following abdominal imaging. (2) Therefore, patients are often referred to urologists for their opinions about diagnosis and management of these lesions. Physicians managing these masses need to distinguish cystic lesions from solid renal masses with necrotic components which behave more aggressively. (3) Hence, the characterization of these cystic renal masses is crucial to determine the best clinical approach to be adopted. We reviewed the literature with the aim to offer guidance to physicians managing these cystic renal lesions and to standardize their management across Canada.
2.0 Methods

A comprehensive search of the literature was done using MEDLINE and Pubmed. A keyword and MeSH search were used to identify English and French publications from January 1st, 1980 to June 30th, 2016 relevant to the topic of interest. The search terms were: Bosniak, Bosniak classification, renal cysts, renal cell carcinomas, renal and kidney cancers. Prospective or retrospective studies as well as review studies providing data on the classification, management and outcomes of complex cystic renal masses were included. Reports limited to children or animal and basic science studies were excluded. Similarly reports limited to congenital or acquired renal cystic diseases and case reports of 5 or fewer cases were also excluded (Appendix 1).

The International Consultation of Urologic Disease (ICUD)/WHO modified Oxford Center for Evidence-Based Medicine grading system was used to grade the quality of evidence for each topic assessed. The level of evidence was summarized according to the following: Level 1-Meta-analysis of randomized-controlled trials (RCTs) or a good-quality RCT; Level 2-Low-quality RCT or meta-analysis of good-quality prospective cohort studies; Level 3-Good-quality retrospective case-control studies or case series; Level 4- Expert opinion. Based on these levels of evidence, we have graded recommendations as follows: Grade A: consistent with level 1 evidence; Grade B: Consistent with level 2 or 3 evidence; Grade C: ‘majority’ evidence from level 2 or 3 studies or level 4 evidence; Grade D: no recommendation possible or expert opinion without a formal analytic process. Importantly, all recommendations were based on expert review of the literature and represent the consensus of all coauthors of these guidelines.

The objectives of these guidelines were to systematically review the literature and to make recommendations on the characterization, management and follow-up of incidentally discovered cystic lesions. The panel proceeded with full awareness of the limitations of the cystic renal
lesions literature. The low quality evidence made it difficult to make strong recommendations for the optimal treatment and follow-up of cystic renal lesions. Furthermore, as the majority of Bosniak category II and IIF cystic lesions were managed conservatively, the literature tends to overestimate the true malignancy risk of these lesions as only the most ‘complex’ ones undergo surgery. Nevertheless, while taking these limitations into account, the panel did its best to summarize the current literature and to provide some guidance of the management of these cystic lesions.
3.0 Evidence synthesis

3.1 Bosniak classification - introduction

Renal cysts can be easily identified using standard medical imaging and, in most of the cases, a histological diagnosis is not required. However, lesions that are more complex may require a more detailed characterization to allow for determination of differential diagnoses and subsequent management approach.

The Bosniak renal cyst classification was initially described in 1986(4) and was later updated to add a new category called category IIF(5). It was originally described using CT imaging, but other modalities, such as MRI, ultrasound (US) or contrast-enhancement ultrasound (CEUS), are now being used to help better delineate these lesions.(6-10) The panel believes that if a complex cyst is first identified on US, contrast-enhanced axial imaging should be performed to better characterize the cyst. (Level of evidence: 4; Recommendation: D)

Although, the Bosniak classification remains the most commonly used classification to characterize renal cysts, it has traditionally been subject to poor inter-observer agreement.(5, 11-17). Nevertheless, a recent report by Graumann et al. has validated the reproducibility of the updated classification in a large cohort.(14) The authors demonstrated very good inter-observer and intra-observer variation among uro-radiologists. Most of the observed variation was seen among cysts categorized as Bosniak II, IIF and III. It is the panel’s opinion that when there is disagreement or doubt regarding the classification of a renal cyst, such case should be presented at a multi-disciplinary meeting. (Level of evidence: 4; Recommendation: D)

3.2 Description of Bosniak Classification
By means of the Bosniak Classification, renal cystic lesions can be categorized in increasing order according to risk of malignancy as follows (Table 1):

**Bosniak category I:**

Lesions classified as category I are simple renal cysts and represent the majority of renal lesions detected by abdominal imaging. These lesions are characterized by their regular contour and a clear interface with the renal parenchyma. They do not contain any septa, calcifications nor do they demonstrate enhancement following intravenous contrast agent injection. They are homogeneous with fluid attenuation varying from 0-20 HU on CT scan. These lesions are also easily identifiable by US and appear as thin walled, anechoic lesions with posterior enhancement and sharply margined smooth walls.

**Bosniak category II:**

These cysts are slightly more complex than category I cysts. They may present with a few hairline-thin septa (<1mm) and may have some calcifications [usually small (1-2mm), linear, parietal or septal]. Small hyperdense cysts (<3cm in diameter and >20 HU) are also classified in this category. These cysts also do not typically show contrast enhancement on imaging.

The majority of category II cysts are considered benign. Although the review of the literature has demonstrated that approximately 11% of the operated category II cysts are malignant, this is thought to be an overestimation of the true malignancy risk as a significant proportion of these studies were published before the addition of the Bosniak IIF category and many of these cysts were managed conservatively without pathological confirmation (Table 2). If we exclude the earlier studies and believe that most of the conservatively managed cysts were benign, the risk of malignancy for these lesions would be less than 5%. This rate is still believed to be a gross overestimation of the true risk as most of the malignant category II lesions had features that made them too complex to be considered a true category II cyst.
**Bosniak category IIF:**

This newest category was added by Dr. Bosniak to decrease the rates of malignancy in category II and to decrease the rate of benign disease in category III.(5) This category represents moderately complex cystic lesions that cannot be unequivocally classified as category II or III cysts. They may contain an increased number of thin septa or a slightly thickened, but smooth septa. Thick or nodular calcification may also be present, but without contrast-enhancing features. Large hyperdense cysts (≥3cm and >20 HU) also belong to this group.(20-22) Any lesions not fulfilling the criteria for category II, but not as complex as category III should be classified in this category.

Similar to the previous two categories, most of the cysts classified in this category are benign. According to our review of the literature, approximately 27% of surgically treated lesions are malignant. However, because of the aforementioned limitations, this is likely an overestimation of the true malignancy risk. If all conservatively managed Bosniak IIF cysts were benign, the risk of malignancy would approach 8%. Therefore, the true malignancy rate of Bosniak category IIF cysts likely falls somewhere between 8 to 27% (Table 2).

**Bosniak category III:**

This category encompasses a variety of cystic lesions whose differentiation between malignant and benign cannot be reliably made by imaging.(5) They present with wall irregularity and thickening as well as wall nodularity. They may also demonstrate contrast-enhanced septa (usually multiple) that are usually irregular, thickened and/or calcified. A significant proportion of these cysts are thought to be malignant (mean of 54%; Table 2)(6, 11-13, 15, 20-48), with larger lesions being more likely to be malignant than smaller ones.(47, 49)
**Bosniak category IV:**

Cysts may have similar characteristics to those classified as category III. They usually demonstrate wall thickening and/or gross and nodular thickened septa, but a solid contrast-enhancing component is also observed adjacent to the cyst wall or septa.\(^{(5, 13, 18, 19, 22, 50)}\) Lesions in this category should be considered malignant until proven otherwise (mean of 88%; Table 2).\(^{(5, 22, 51)}\).

**3.3 Intervention and follow-up**

**Bosniak category I:**

This category is composed of simple cysts which are considered benign. One should remember that the natural history of these cysts is that the majority will grow over time and thus, growth should not necessarily be considered a sign a malignancy.\(^{(52, 53)}\) Transformation into a more complex cyst is rare and has been reported in only a handful of cases.\(^{(52-57)}\) As this is rare in occurrence, these cysts do not require follow-up. **(Level of evidence: 3; Recommendation: B)**

Intervention is only warranted if the cyst becomes symptomatic (i.e. bleeding, recurrent infection or pain), in which case treatment options include: percutaneous management (aspiration +/- sclerotherapy) or surgery.\(^{(58)}\) **(Level of evidence: 3; Recommendation: B)** Percutaneous cyst decompression may also be considered prior to offering definitive treatment as a means to confirm that the source of symptoms are cyst-related. (Level of evidence: 4; Recommendation: D)

**Bosniak category II:**
These minimally complex cysts are also generally considered benign but there are reports in the literature of category II lesions being malignant (Table 2). (11, 12, 15, 23-27, 31, 33, 34, 39, 40, 42, 43, 47, 51, 59) However, the literature is thought to overestimate the true risk of malignancy among category II cysts as the majority were managed conservatively or had features that made them too complex to be categorized as a Bosniak II cyst. (6, 12, 26, 29, 31, 32, 35, 38, 59) Importantly, even if malignant, most behave in a relatively benign fashion (refer to section 3.4). Consequently, similar to category I cysts, a follow-up for properly classified Bosniak II cysts is not warranted (Level of evidence: 3; Recommendation: C) and intervention is not recommended unless the patient is symptomatic. (Level of evidence: 3; Recommendation: B)

When there is doubt as to their categorization based on imaging characteristics, these lesions should be considered as being Bosniak category IIF lesions and followed accordingly.

**Bosniak category IIF:**

Given the relatively high risk of malignancy among these cysts (Table 2), as the ‘F’ in category IIF stipulates, these lesions require ‘follow-up’. (Level of evidence: 3; Recommendation: B) Approximately 15% of these category IIF cysts will progress in complexity (to Bosniak category III or IV) over time. (7, 13, 20, 21, 36) Progression is more likely to occur within the first 2 years and rarely occurs after 5 years. (36) Unfortunately, a clear progression pattern is yet to be identified and as a result, there is no evidence-based time limit for follow-up imaging. In view of the low-metastatic potential of these lesions (if malignant), it seems reasonable to follow these lesions with a contrast-enhanced CT scan or MRI every 6 months for the first year. (Level of evidence: 4; Recommendation: D) Closer monitoring may be performed, but may potentially reduce the detection of a progression if the changes in the cysts from imaging to imaging are very small. CEUS may also be used to better delineate the septa number, septa and/or wall thickness, solid component and the enhancement. (8, 10, 60) Ultrasound in combination with CT or MRI
may be used if the lesion is stable on follow-up. Cases without progression should be followed annually for at least 5 years. (Level of evidence: 4; Recommendation: D)

**Bosniak category III:**

Studies of resected Bosniak III lesions have found approximately 54% (IQR: 44-67%) of these cysts to be malignant (Table 2). Based on current evidence, surgical excision of Bosniak III cysts is generally suggested. (Level of evidence: 3; Recommendation: B) Extrapolating from small renal mass (SRM) data, partial nephrectomy (PN) is considered the treatment of choice when feasible, if surgery is planned. (Level of evidence: 2; Recommendation: B) Given the low-metastatic potential of cystic RCCs, the panel feels that reduced surgical margins and controlled cyst decompression (if required) can be performed with low risk of tumor recurrence. (Level of evidence: 4; Recommendation: D) Likewise, due to the same reason, active surveillance and thermal-ablation therapies may also be considered as appropriate treatment alternatives in select cases (further discussed below). (Level of evidence: 4; Recommendation: D)

**Bosniak category IV:**

The majority of the lesions included in this category are malignant (Table 2) with over 80-90% of Bosniak category IV lesions being cystic RCCs. (6, 11-13, 15, 23, 25, 29, 31-35, 38-40, 42-44, 48) Surgical excision is generally suggested (Level of evidence: 3; Recommendation: B) with PN being the surgery of choice, when feasible. (Level of evidence: 2; Recommendation: B) Nevertheless, most of these malignant cysts are thought to have low-metastatic potential and thus, more conservative management may be safely considered in select cases. (Level of evidence: 4; Recommendation: D)
3.4 Role of Active Surveillance for suspected cystic RCC

Physicians managing cystic RCCs need to distinguish them from solid renal masses with necrotic components which behave more aggressively.(3) Cystic RCCs are part of a spectrum of complex cystic renal masses that are known to have an increased risk of malignancy with increasing complexity (i.e.: Bosniak classification III and IV cysts). The vast majority of cystic RCCs are multilocular cystic RCCs (mcRCC)(62), but all RCC subtypes may present in a predominantly cystic form.(63) Although, the suggested treatment of choice for these lesions remains surgical excision, there is increasing evidence that they have relatively low-metastatic potential and carry an excellent prognosis.(63-67) To the best of our knowledge, there is yet to be a report demonstrating metastases or recurrence of these lesions. To reflect this indolent behavior, the International Society of Urological Pathology (ISUP) has recently modified its terminology and now recommends calling these lesions multilocular cystic renal neoplasm with low malignant potential.(62)

Several studies have compared their prognosis to that of solid RCCs. mcRCCs have consistently fared better than their counterparts on both cancer-specific and overall survival.(24, 66-73) One potential explanation for this better prognosis is that the majority of mcRCCs tumor volume is fluid and thus, the actual tumor burden is much lower when compared to similar-sized solid tumors.(67) As the outcomes of these tumors do not seem to be influenced by the overall lesion size, some experts have even suggested to abandon the current pathological T staging for mcRCC and to reassigned them a new stage called pT1c (c for cystic).(67)

Given their relatively indolent nature, there is emerging evidence suggesting that these lesions (especially Bosniak classification III) can be safely managed by active surveillance.(6, 12, 13, 29, 31, 32, 35, 38, 41, 48, 59). Extrapolating from data on SRMs, Bhatt et al. have suggested that Bosniak III and perhaps even Bosniak IV cysts with a solid component measuring less than 3cm could be managed with initial surveillance.(67) Nevertheless, given the paucity of data, this
management strategy should be reserved for well-informed patients and generally for patients at high surgical risk due to comorbidities or limited life expectancy. (Level of evidence: 4; Recommendation: D) There is currently no evidence to dictate any specific follow-up scheme. However, if active surveillance is considered, it seems reasonable to follow these lesions with abdominal imaging every 6 months for the first 2 years followed by yearly imaging thereafter, if the lesion is stable. (Level of evidence: 4; Recommendation: D) Likewise, triggers for interventions are yet to be clearly defined and validated, but may include progression from Bosniak III to IV, growth of solid nodule over 3cm and fast growing nodule. (Level of evidence: 4; Recommendation: D)

3.5 Thermal-ablation therapies

The current standard of care for the management of Bosniak category III and IV cysts remains surgical excision, but thermal-ablation therapies may be considered as an alternative in select cases. Data supporting this approach is mostly extrapolated from the management of solid SRMs.(61) Nevertheless there is some evidence from small case series supporting radiofrequency ablation (RFA) as a treatment alternative.(74-78) Overall, given the limited data, RFA should be limited to patients with small Bosniak category III and IV cysts who are poor operative candidates and in whom active surveillance is not being considered. (Level of evidence: 3; Recommendation: C) To the best of our knowledge, the role of cryotherapy in the management of Bosniak III or IV cysts is not well defined with only a handful of cases reported to have been treated by the approach in the literature.(36) Patients opting for the treatment alternative should be made aware of the sparse literature on the management of cystic renal lesions using these approaches. The role of renal tumor biopsy (RTB) should also be discussed with these patient prior to treatment. (Level of evidence: 3; Recommendation: C)

3.6 Role of renal tumor biopsy in the management of cystic lesions
There is now substantial evidence supporting the role of RTB for the pretreatment identification of the histology of solid renal masses. (79, 80) RTB is safe, accurate and reliable. Additionally, needle core biopsy has been shown to decrease overtreatment rates when used in the management of solid small renal masses. (80, 81) However, its role in the management of cystic renal masses is not clearly defined.

There is evidence that RTBs are significantly less informative for the diagnosis of cystic lesions than for solid ones. (79, 82-84) Therefore, the utility of RTB in cystic lesions is less than that observed with solid SRMs. Nevertheless, there is literature supporting the role of RTB for histology identification of Bosniak III and IV cysts. (28, 74, 75, 82) It is generally felt that RTB is not diagnostic for most Bosniak III cysts as there is minimal targetable solid component. (Level of evidence: 3; Recommendation: D) For Bosniak IV cysts, a biopsy of the solid component may be considered to confirm the presence of a malignant tumor and to help with decision-making in select cases (elderly, multiple comorbidities, unfit for treatment, etc). (5, 28, 74, 75, 82, 83) (Level of evidence: 3; Recommendation: C) Of interest, some reports have suggested that the combination of fine needle aspiration (FNA) and core biopsy may lead to a slightly higher diagnostic yield than core biopsy alone. (85) Nevertheless, in most centers of experience, RTB are performed using core biopsy alone as the combination is thought to add minimal value. Experts have also reported a higher diagnostic rate in Bosniak IV cyst when the solid component was greater than 1cm. (83)

4.0 Conclusions

The evidence for optimal management of cystic RCC including follow-up, is low quality and based on case series and indirectly from the management of solid SRMs. Nevertheless, these guidelines provide some guidance to urologists on how to best manage and follow these cystic lesions. In summary, Bosniak category I and II cysts do not routinely require follow-up whereas Bosniak category IIF cysts should be followed with routine imaging. Although surgical excision
is still recommended for Bosniak category III and IV cysts, there is growing evidence suggesting that alternate management can be safely considered in select cases.

5.0 References

5. Bosniak M. Diagnosis and Management of Patients with Complicated Cystic Lesions of the Kidney. AJR. 1997;169:819-21.

6.0 Tables

Table 1. The Bosniak classification and management recommendations

<table>
<thead>
<tr>
<th>Bosniak Classification – key findings</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bosniak category I (simple renal cyst)</strong></td>
<td></td>
</tr>
<tr>
<td>• Usually round or oval shape</td>
<td>• No follow-up required</td>
</tr>
<tr>
<td>• Anechoic with posterior enhancement on U/S</td>
<td></td>
</tr>
<tr>
<td>• Regular contour with clear interface with renal parenchyma</td>
<td></td>
</tr>
<tr>
<td>• No septa, calcification or enhancement</td>
<td></td>
</tr>
<tr>
<td><strong>Bosniak category II</strong></td>
<td></td>
</tr>
<tr>
<td>• Thin septum (&lt;1mm)</td>
<td>• No follow-up required</td>
</tr>
<tr>
<td>• Fine calcification (often small, linear, parietal or septal)</td>
<td></td>
</tr>
<tr>
<td>• Small hypodense cyst (&lt;3cm; &gt;20 HU)</td>
<td></td>
</tr>
<tr>
<td>• No perceived contrast enhancement</td>
<td></td>
</tr>
<tr>
<td><strong>Bosniak category IIF</strong></td>
<td></td>
</tr>
<tr>
<td>• Cyst unequivocally categorized as category II or III cysts</td>
<td>• Follow-up recommended</td>
</tr>
<tr>
<td>• Multiple thin septa or a slightly thickened but smooth septa</td>
<td>• Imaging at 6 months and 12 months after diagnosis and then annually for at least 5 years if no progression.</td>
</tr>
<tr>
<td>• Calcifications – thick or nodular</td>
<td></td>
</tr>
<tr>
<td>• No perceived contrast enhancement</td>
<td></td>
</tr>
<tr>
<td>• Large hyperdense cysts (≥3cm)</td>
<td></td>
</tr>
<tr>
<td><strong>Bosniak category III</strong></td>
<td></td>
</tr>
<tr>
<td>• Uniform wall thickening and/or nodularity</td>
<td>• Surgical excision is suggested</td>
</tr>
<tr>
<td>• Irregular, thickened and/or calcified septa</td>
<td>• Conservative management and RFA in select cases</td>
</tr>
<tr>
<td>• Contrast-enhancing septa</td>
<td></td>
</tr>
<tr>
<td><strong>Bosniak category IV</strong></td>
<td></td>
</tr>
<tr>
<td>• Wall thickening</td>
<td>• Malignant until proven otherwise</td>
</tr>
<tr>
<td>• Gross, irregular and nodular septal thickening</td>
<td>• Surgical excision is suggested</td>
</tr>
<tr>
<td>• Solid contrast-enhancing component, independent of septa</td>
<td>• Potential role for pretreatment RTB (of solid component) to confirm malignancy</td>
</tr>
<tr>
<td></td>
<td>• RFA and conservative management in select cases</td>
</tr>
<tr>
<td>Authors (year of publication)</td>
<td>Cohort size N (path. confirmed)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Brown (1989)</td>
<td>24 (24)</td>
</tr>
<tr>
<td>Aronson (1991)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Wilson (1995)</td>
<td>24 (24)</td>
</tr>
<tr>
<td>Cloix (1996)</td>
<td>32 (32)</td>
</tr>
<tr>
<td>Siegel (1997)</td>
<td>70 (70)</td>
</tr>
<tr>
<td>Bielsa (1999)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Curry (2000)</td>
<td>116 (82)</td>
</tr>
<tr>
<td>Koga (2000)</td>
<td>35 (35)</td>
</tr>
<tr>
<td>Limb (2002)</td>
<td>57 (57)</td>
</tr>
<tr>
<td>Harisinghani (2003)</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Israel (2003)</td>
<td>81 (40)</td>
</tr>
<tr>
<td>Israel (2003)</td>
<td>42 (3)</td>
</tr>
<tr>
<td>Israel (2004)</td>
<td>69 (25)</td>
</tr>
<tr>
<td>Spaliviero (2005)</td>
<td>47 (47)</td>
</tr>
<tr>
<td>Lee (2006)</td>
<td>53 (17)</td>
</tr>
<tr>
<td>Quaia (2007)</td>
<td>40 (30)</td>
</tr>
<tr>
<td>Clevert (2008)</td>
<td>37 (14)</td>
</tr>
<tr>
<td>Song (2008)</td>
<td>104 (104)</td>
</tr>
<tr>
<td>Gabr (2009)</td>
<td>50 (7)</td>
</tr>
<tr>
<td>O’Malley (2009)</td>
<td>112 (34)</td>
</tr>
<tr>
<td>Kim (2010)</td>
<td>125 (125)</td>
</tr>
<tr>
<td>Pinheiro (2011)</td>
<td>37 (37)</td>
</tr>
<tr>
<td>Weibl (2011)</td>
<td>113 (69)</td>
</tr>
<tr>
<td>You (2011)</td>
<td>75 (75)</td>
</tr>
<tr>
<td>Smith AD (2012)</td>
<td>213 (123)</td>
</tr>
<tr>
<td>Han (2012)</td>
<td>98 (98)</td>
</tr>
<tr>
<td>Graumann (2013)</td>
<td>32 (3)</td>
</tr>
<tr>
<td>El-Mokadem (2014)</td>
<td>154 (39)</td>
</tr>
<tr>
<td>Kim (2014)</td>
<td>164 (85)</td>
</tr>
<tr>
<td>Hindman (2014)</td>
<td>156 (19)</td>
</tr>
<tr>
<td>Reese (2014)</td>
<td>113 (113)</td>
</tr>
<tr>
<td>Xu (2014)</td>
<td>87 (87)</td>
</tr>
<tr>
<td>Smith (2015)</td>
<td>286 (100)</td>
</tr>
<tr>
<td>Oh (2016)(47)</td>
<td>324 (324)</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3032 (2106)</strong>‡</td>
</tr>
</tbody>
</table>

*Studies limited to the ones where complex lesions were also evaluated.

‡Overall, 142 Bosniak category II, 668 Bosniak category IIF, 115 Bosniak category III and 21 Bosniak category IV were managed by surveillance

†Represent an overestimation of the true malignancy risk given the fact that the majority of lesions were managed with surveillance.

## 7.0 Appendix

Appendix 1: Flow diagram: Search and study selection process

![Flow diagram: Search and study selection process](image)