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Medical Policy Manual

Topic: Saturation Biopsy for Diagnosis and Staging of Prostate Cancer

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Section: Surgery

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Saturation biopsy involves obtaining at least 20 biopsy tissue cores from the prostate in a systematic manner. Use of saturation biopsy has been proposed for use in the diagnosis (for initial or repeat biopsy), staging, and management of patients with prostate cancer.

Prostate cancer is a common cancer and is the second leading cause of cancer-related deaths in men in the U.S. The diagnosis of prostate cancer is made by biopsy of the prostate gland. The approach to biopsy has changed over time, especially with the advent of PSA (prostate-specific antigen) screening programs that identify cancer in prostates that are normal to palpation and to transrectal ultrasound. For patients with an elevated PSA-level but with a normal biopsy, questions exist about subsequent evaluation since repeat biopsy specimens may be positive for cancer in a substantial percentage of patients.

In the early 1990s, use of sextant biopsies involving six random, evenly distributed biopsies became the standard approach to the diagnosis of prostate cancer. In the late 1990s, as studies showed high false-negative rates for this strategy (missed cancers), approaches were developed to increase the total number of biopsies and to change the location of the biopsies. While there is disagreement about the optimal strategy, most would agree that initial prostate biopsy strategies should include at least 10–14 cores. Additional concerns have been raised about drawing conclusions about the stage (grade) of prostate

cancer based on limited biopsy material. Use of multiple biopsies has also been discussed as an approach to identify tumors that may be eligible for subtotal cryoablation therapy.

At present, many practitioners use a 12 to 14 core "extended" biopsy strategy for patients undergoing initial biopsy. This extended biopsy is done in an office setting and allows for more extensive sampling of the lateral peripheral zone; sampling of the lateral horn may increase the cancer detection rate by approximately 25%.[1]

Another approach to increase the number of biopsy tissue cores is use of the "saturation" biopsy. In general, saturation biopsy is considered as a minimum of 20 cores taken from the prostate, with improved sampling of the anterior zones of the gland which may be under-sampled in standard peripheral zone biopsy strategies and may lead to cancers being missed.[2]

Saturation biopsy may be performed transrectally or with a transperineal approach; the transperineal approach is generally performed as a stereotactic template-guided procedure with general anesthesia.

MEDICAL POLICY CRITERIA

Saturation biopsy, taking 20 or more core tissue samples at one time, is considered **investigational** in the diagnosis, staging, and management of prostate cancer.

SCIENTIFIC EVIDENCE[3]

In order to evaluate the use of saturation biopsy as an appropriate method of initial or repeat screening, tumor assessment or to identify local disease, the scientific evidence must demonstrate how the results of saturation biopsy can be used to benefit patient management and impact health outcomes (i.e., clinical utility) compared with the extended biopsy. Specifically, studies are needed which assess whether additional biopsy cores from saturation biopsy result in the identification of clinically significant prostate cancers and how these findings improve treatment decisions. Randomized trials are needed to reliably make these comparisons and demonstrate the impact of the test on net health outcomes. To date, no studies were identified that link the use of saturation biopsy to clinical outcomes. In addition, the majority of studies were case series of patients who underwent saturation biopsy, rather than comparative studies of various biopsy techniques.

Initial Biopsy

Meta-Analysis and Systematic Reviews

- In 2013, Jiang and colleagues published a systematic review and meta-analysis of studies evaluating the utility of an initial transrectal saturation biopsy compared to an extended biopsy strategy.[4] A total of 8 studies with 11,997 participants met eligibility criteria which included a comparison of the two biopsy strategies on initial biopsy. Two of the studies were randomized controlled trials (RCTs), 1 used a paired design and 5 were non-randomized controlled studies. Overall, prostate cancer detection rate was statistically significantly higher (p=0.002) in the saturation biopsy group (2,328 of 5,486 men; 42.4%) compared to men who had extended biopsy

(2,562 of 6,511 men; 39.3%). When only the higher quality studies were included in the meta-analysis (the RCTs and prospective paired design), the detection rate was again statistically significantly higher with saturation biopsy (p=0.01).

In a subgroup analysis, the prostate cancer diagnosis rate was statistically significantly higher (p=0.002) in patients with PSA <10 ng/mL in the saturation biopsy group (998 of 2,597 men; 38%) compared to the extended biopsy group (1,135 of 3,322 men; 34%). However, the clinical significance of this degree of difference is unclear. There was not a statistically significant difference between groups in the diagnostic yield for men with PSA >10 ng/mL (p=0.15). Although the authors found statistically significantly higher rates of diagnosis in their overall pooled analyses, the degree of difference in diagnosis rates may not be clinically significant.

- In 2013, Bjurlin and colleagues published a systematic review evaluating the prostate biopsy process to assess the ideal method for obtaining and processing specimens.[5] A variety of outcomes were considered, including the optimal number and location of biopsy cores during primary biopsy among men suspected of prostate cancer. Authors concluded that use of 10-12 core extended sampling increases rates of cancer detection over sextant sampling; however, an increase in the number of cores above 12 resulted in a marginal diagnostic yield. In addition, the authors concluded that, "This literature review does not provide compelling evidence that individual site specific labeling of cores benefits clinical decision making regarding the management of prostate cancer."

Randomized Controlled Trials (RCTs)

Other than the RCTs noted above in the systematic review by Jaing and colleagues, no other RCTs were identified regarding saturation biopsy as an initial screening for prostate cancer.

Nonrandomized Trials

A number of studies have compared the yield (finding prostate cancer) and have not found that use of saturation biopsy improves cancer detection rates compared with extended biopsy strategies. Authors suggested that large, easy-to-identify tumors in the general population are usually identified without a need for saturation biopsy. For example, Ashley performed a study of 469 consecutive prostate biopsies to determine whether saturation biopsy (at least 24 cores) that was performed in 168 patients detected more prostate cancer than a standard 12–18 core office biopsy technique.[6] After adjustments for covariates, saturation biopsy did not detect more prostate cancer (odds ratio 1.2; p=0.339). The authors concluded that saturation biopsy did not appear to detect more abnormal prostate pathology than the control.

- More recently, Li and colleagues reviewed data on 438 men who received and initial saturation biopsy and 3,338 men who had an initial extended prostate biopsy.[7] In an analysis stratified by PSA values, there was a statistically significantly higher rate of prostate cancer detection using a saturation biopsy strategy in men with a prostate-specific antigen (PSA) less than 10 ng/mL. Detection rates among men with PSA less than 4 ng/mL were 47.1% with saturation biopsy (40/85) and 32.8% with extended biopsy (288/878), p=0.008. Rates among men with PSA between 4 and 9.9 ng/mL were 50.9% with saturation biopsy (144/283) and 42.9% with extended biopsy (867/2,022), p=0.011. There was not a statistically significant difference in detection rates between groups when PSA was greater than 10 ng/mL. Detection rates in men with PSA greater than 10/ng/mL were 60% with saturation biopsy (42/70) and 61% with extended biopsy

(267/438), p=0.879. However, the impact these improvements have upon health outcomes has yet to be demonstrated, leaving the efficacy of saturation biopsy at initial biopsy in question.

- In a nonrandomized retrospective study by Merrick and colleagues, template-guided saturation biopsy (TTSB) was examined in 102 patients with a previous negative TRUS-guided biopsy and elevated PSA or multifocal high-grade prostate intraepithelial neoplasm (PIN).[8] The prostate gland was divided into 24 regional locations and a median of 50 cores were taken. Prostate cancer was detected in 43 patients (42.2%) with a Gleason score of 6-9. Prostate cancer was found in 43 patients (42.2%) in an average of 9.9 cores. Although the overall detection of cancer was high, these results should be considered with caution as they are from a nonrandomized trial and were not compared to other standard of care cancer detection methods.

Conclusion

The evidence regarding the benefits of saturation biopsy as an initial screening technique for detecting prostate cancer is inconsistent. Although one systematic review and several nonrandomized trials demonstrated a higher rate of cancer diagnosis with saturation biopsy over standard biopsy, the significance of these findings on treatment management and survival rates have not been evaluated. Studies which demonstrate how saturation biopsy leads to improved outcomes, such as an increased detection in clinically significant cancers, are needed in order to determine the efficacy of increasing the number biopsies.

Repeat Biopsy

Meta-Analysis and Systematic Reviews

Eichler and colleagues conducted a systematic review of cancer detection rates and complications of various prostate biopsy schemes.[9] They pooled data that compared various extended biopsy schemes in studies involving a total of 20,698 patients. These authors concluded that prostate biopsy schemes consisting of 12 cores that add laterally directed cores to the standard sextant scheme seems to have the right balance between the cancer detection rate and adverse events and that taking more than 12 cores added no significant benefit.

Randomized Controlled Trials (RCTs)

No RCTs were identified regarding saturation biopsy as a repeat screening technique for detection of prostate cancer.

Nonrandomized Trials

- Mabjeesh and colleagues reported on a high-risk group of men with at least 2 previous negative transrectal biopsies who then underwent transperineal template-guided saturation biopsy.[10] Prostate cancer was detected in 26% of the 92 patients, predominantly in the anterior zones. A median of 30 cores was taken in the saturation biopsies. Gleason score of equal to or greater than 7 was detected in 46% of the diagnosed men. Most of the tumors (83.3%) were found in the anterior zones of the gland, with a significantly higher number of positive cores versus the posterior zones (mean 4.9 vs. 1.5, p= 0.015).

- Lee and colleagues evaluated the role of transrectal saturation biopsy for cancer detection in men with high-grade prostatic intra-epithelial neoplasia (HGPIN) diagnosed by extended biopsy.[11] From 1999 to 2009, 314 men had at least 1 or more repeat biopsies due to the presence of exclusive HGPIN (without any other pathologic finding) in a previous extended biopsy. They were divided into 2 groups according to the initial follow-up biopsy scheme; 178 men were followed up using a second standard extended biopsy scheme, and 136 were followed up using the saturation biopsy scheme. In the standard repeat biopsy group, 35 of 178 (19.7%) men had cancer on initial repeat biopsy. In the saturation biopsy group, 42 of 136 (30.9%) had cancer on initial repeat biopsy (overall, p=0.04). Multivariate analysis demonstrated that the biopsy scheme on repeat biopsy was an independent predictor of prostate cancer detection (OR: 1.85, (95% confidence interval [CI]: 1.03, 3.29), exclusive of age, prostate-specific antigen (PSA) level, days from initial biopsy, digital rectal exam (DRE) status, and multifocal prostatic epithelial neoplasia (PIN). Pathologic findings on repeat biopsies demonstrated similar Gleason grades, regardless of biopsy technique: Gleason 6 was present in 74.3% and 73.1% of specimens in the standard and saturation schemes, respectively. The presence of a Gleason score of 8 or higher was 8.6% and 9.5%, respectively.

- Giulianelli and colleagues evaluated whether or not the saturation biopsy technique increased the cancer detection rate in patients with PSA less than 10 ng/mL, after a first negative biopsy.[12] From January 2004 to January 2006, 780 patients underwent prostate ultrasound-guided transrectal core biopsies: 186 (23.8%) were diagnosed with prostate cancer, while 594 (76.2%) had negative biopsies. For 1 year, all of the patients with no evidence of cancer were observed according to a follow-up schedule including PSA every 3 months and DRE every 6 months. During this period, 140 patients showed an increase of PSA (<10 ng/mL) or a low PSA free/total. This group underwent a second ultrasound-guided transrectal core biopsy with saturation technique under general anesthesia. Of the 140 patients, 50 (35.7%) had prostate cancer showing a Gleason score of 4 or 5 in 26%, 6 or 7 in 75%, and 8 to 10 in 9%, respectively. Apical biopsies carried out in the anterior horn of peripheral zone tissue showed cancer in 35 patients (70% of those rebiopsied), versus 24% in lateral zones, and 5% for parasagittal. Cancer in the patients who underwent the saturation biopsy was considered clinically significant (defined as Gleason score of $\geq$7 and tumor volume >0.5 cc) in 47 patients (94%). Forty-eight of 50 underwent a radical prostatectomy and 2 underwent external beam radiation therapy. The authors concluded that the saturation biopsy technique increased the cancer detection rate by 36% in patients with PSA less than 10 ng/mL, after a first negative biopsy, and showed a higher positivity (70% prostate cancer detection rate) if the saturation biopsy included the anterior horn of peripheral zone tissue. No significant pain or side effects were observed.

- Simon and colleagues reported on the results using an extensive saturation biopsy in 40 men with a clinical suspicion of prostate cancer after previous negative prostate biopsies.[13] The median number of cores taken was 64 (range: 39–139) and was adjusted to the size of the prostate. Of the 40 men, 18 (45%) had cancer in at least one core. Sixteen men had marked hematuria after the biopsy procedure. The investigators concluded there was no significant increase in the cancer detection rate with this extensive saturation biopsy regimen compared to published series with fewer cores, but there was increased morbidity.

- Zaytoun and colleagues reported the results of a prospective, non-randomized comparative study of extended biopsy versus office-based transrectal saturation biopsy in a repeat biopsy population.[14] After an initially negative biopsy, 1,056 men underwent either a repeat 12- to 14-

core biopsy (n=393) or a 20- to 24-core repeat biopsy (n=663) at the discretion of the attending urologist's practice pattern. Indications for second biopsy included a previous suspicious pathologic finding and/or clinical indications such as abnormal digital rectal examination, persistently increased prostate-specific antigen (PSA), and PSA increasing greater than 0.75 ng/mL annually. Prostate cancer was detected in 29.8% (n=315) of repeat biopsies. The saturation biopsy group had a detection rate of 32.7% versus 24.9% in the extended biopsy group (p=0.0075). Of the 315 positive biopsies, 119 (37.8%) revealed clinically insignificant cancer (defined as Gleason sum <7, a total of 3 or fewer positive cores, and a maximum of 50% or less of cancer in any positive core). There was a trend toward increased detection of clinically insignificant cancer detection in the saturation versus the extended biopsy cases, 40.1% versus 32.6%, respectively (p=0.02).

- Linder and colleagues reviewed data on 500 consecutive patients who underwent standard template prostate biopsy (12 cores) or saturation biopsy (at least 18 cores) prior to radical prostatectomy.[15] The authors identified 218 patients who would have been candidates for active surveillance. Criteria were Gleason score no greater than 6, clinical stage T1 or T2a, PSA <10 ng/ml and involvement of no more than 33% of cores. Among these 218 patients, 124 had undergone standard biopsy and 94 underwent saturation biopsy. In a multivariate analysis, biopsy method was not a significant predictor of upstaging upon analysis of pathological findings (p=0.26). In addition, the 5-year biochemical failure-free survival rates (defined as PSA at least 0.4 ng/ml) were not significantly different in the 2 groups: rates were 97% for standard biopsy and 95% for saturation biopsy (p=0.11). The authors concluded that standard biopsy and saturation biopsy are equally effective for identifying candidates for active surveillance.

Conclusion

Current studies in patients with a previous negative prostate biopsy suggested an increased detection rate with saturation biopsy compared with standard sampling. However, this evidence is from nonrandomized trials which have not shown whether saturation biopsy leads to detection of clinically significant cancers or an overall improvement in health outcomes. Questions remain regarding patient selection, optimal technique, number of biopsy cores and strategy regarding sampling region. Evidence from randomized controlled trials (RCTs), which compare the saturation technique to other methods of prostate cancer detection, are needed in order to limit bias and confounding factors.

Localized Disease

There also are discussions of using saturation biopsy as a technique to identify a localized area of prostate cancer that could be treated with subtotal cryoablation. However, given the limited data on the efficacy of this treatment approach, using saturation biopsy to determine if localized disease is present is considered investigational.

Active Surveillance

In men whose cancers are small and expected to behave indolently, active surveillance with PSA, DRE, and routine prostate biopsies may be recommended. Saturation biopsy is proposed as a possible method to more accurately assess tumor volume and/or tumor grade; however, there are no studies that link this potential use to improved outcomes.

Ayres and colleagues evaluated the role of transperineal template prostate biopsies in 101 men on active surveillance for prostate cancer.[16] The men underwent restaging transperineal template prostate biopsies at a single center. The criteria for active surveillance were: age 75 years or younger, Gleason ≤3+3, PSA ≤15 ng/mL, clinical stage T1-2a, and ≤50% ultrasound-guided transrectal biopsy cores positive for cancer, with ≤10 mm of disease in a single core. The number of men with an increase in disease volume or Gleason grade on transperineal template biopsy and the number of men who later underwent radical treatment were assessed. The roles of PSA and PSA kinetics were studied. In all, 34% of men had more significant prostate cancer on restaging transperineal template biopsies compared with their transrectal biopsies. Of these men, 44% had disease predominantly in the anterior part of the gland, an area often under-sampled by transrectal biopsies. In the group of men who had their restaging transperineal template biopsies within 6 months of commencing active surveillance, 38% had more significant disease. There was no correlation with PSA velocity or PSA doubling time. In total, 33% of men stopped active surveillance and had radical treatment. The study concluded that around one-third of men have more significant prostate cancer on transperineal template biopsies and that this probably reflects under-sampling by initial transrectal biopsies rather than disease progression.

Improving Correlation between Biopsy and Operative Stage

Similarly, data are lacking on a potential use of saturation biopsy to assist in more accurately assessing tumor grade/stage when the treatment regimen is determined through biopsy rather than through surgical removal of the prostate. Evaluation of such an approach would require either a randomized trial or determining treatment plans for a group of patients based on use of varying numbers of their biopsy specimens.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN) Guidelines

The 2013 NCCN guidelines on prostate cancer early detection state that in patients with 2 negative extended biopsies, yet persistently rising PSA values, a saturation biopsy may be considered.[17] The evidence in support of this recommendation is limited to one observational study.[18]

Summary

Current evidence suggests that saturation biopsy (taking 20 or more tissue cores) may detect prostate cancer at least as well as standard 12-core extended biopsy. However, there is insufficient evidence to determine the impact of the additional tissue cores on treatment management, survival rates, and quality of life. In addition, it is not clear that saturation biopsy leads to an improvement in the detection of clinically significant prostate cancer, which could lead to unnecessary treatment. Therefore, saturation biopsy of the prostate is considered investigational.

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CROSS REFERENCES

Systems Pathology for Predicting Risk of Recurrence in Prostate Cancer, Laboratory, Policy No. 61

CODES	NUMBER	DESCRIPTION
CPT	55706	Biopsies, prostate, needle, transperineal, stereotactic template guided saturation sampling, including imaging guidance
HCPCS	G0416	Surgical pathology, gross and microscopic examination for prostate needle saturation biopsy sampling, 1-20 specimens
	G0417	Surgical pathology, gross and microscopic examination for prostate needle saturation biopsy sampling, 21-40 specimens
	G0418	Surgical pathology, gross and microscopic examination for prostate needle saturation biopsy sampling, 41-60 specimens
	G0419	Surgical pathology, gross and microscopic examination for prostate needle saturation biopsy sampling, greater than 60 specimens