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Urology Pathway Board

PROPOSED REVISION TO ACTIVE SURVEILLANCE GUIDELINES

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Proposed Revision to Active Surveillance Guidelines

Background

The current NW guidelines on AS were written in 2013 and are currently due for review. Moreover, the clinical management of patients on Active Surveillance has changed significantly since these guidelines were written. There has been a significant increase in the use of multi-parametric MRI (mpMRI), particularly in the pre-biopsy setting, but more recently a progressive increase in the rates of the trans-perineal approach for biopsies (both for initial and subsequent investigations). This change in diagnostic pathway has the potential to increase the yield of initial investigations and thereby alter the need for subsequent invasive tests. There has also been a move away from radical treatment for low risk patients, with more and more intermediate risk patients managed with surveillance alone.

As a result of these changes being adopted in some areas, a significant variance in practice has been observed within GM particularly in relation to who is offered active surveillance and how it is carried out. These guidelines are intended to promote evidence based practice which is consistent through the GM area.

The specific issues that require addressing in the updated guidance are;

1) Inclusion criteria. The current guidelines use NICE NG131 risk stratification and states AS is suitable for low or intermediate risk only; this would exclude T2c patients for whom AS may still be appropriate. Other inclusion/exclusion criteria are not addressed, such as biopsy details, risk factors etc. Intermediate risk also includes patients at high risk of progression in other series.

2) Need for confirmatory biopsies. The current guidelines suggest that confirmatory biopsies should be performed at 12 months then every 3 years thereafter. However, the evidence base for this came from studies trans-rectal biopsies both at time of diagnosis and for follow-up biopsies, and this does not necessarily reflect current practice.

3) Surveillance mpMRI. The current guidelines were written before the widespread introduction of mpMRI, particularly in the pre-biopsy setting. The frequency of follow-up imaging is particularly variable throughout the region, which has a potentially significant impact on resources as well as cost.

Suggested Changes

Inclusion Criteria

Low Risk Disease

Active Surveillance should continue to be the recommended treatment option for men with low risk disease and a life expectance of more than 15 years. Low risk for the purpose of the guidelines is defined using NICE NG131 criteria and is defined as PSA<10ng/ml and Gleason score 6 and ≤T2a.Attention should be paid that men with a co-existing genetic pre-disposition (such as BRCA 1, Lynch etc.) should be discouraged from entering AS due to their high risk of progression. Patients with a strong family history of an underlying genetic condition should be referred for genetic assessment prior to commencement of Active Surveillance.

Intermediate Risk disease

AS is an option for the management of intermediate risk disease, though the patient should be fully counselled about the risks of progression and this risk should be quantified in relation to risk factors. The Toronto series demonstrated a significant increase in the development of metastatic disease at 15yrs (16% compared to 6% for all pattern 3), which emphasises the potential risks that need to be discussed with the patient as well as the need for long term follow-up if AS is commenced. Similarly, the Marsden series showed progression could occur at any point, with progression seen up to ten years from initiation of surveillance.

The Cambridge Group proposed 5 prognostic risk groups to further expand and define the risk of progression for patients at diagnosis (with the primary end point being mortality). Cambridge Prognostic Group (CPG) 3 show clearly worse outcomes than CPG 2 patients, yet NICE intermediate group patients could fall into either group 2 or 3. For example, a patient with a Gleason 3+4 tumour and a PSA of 17 would be intermediate group in NICE NG131, whereas this patient would be CPG 3 and as such would have a much higher risk of progression than some other intermediate risk disease patients. It is therefore suggested that CPG 3 patients should not be considered for Active Surveillance without discussion at the SMDT and appropriate modification of the surveillance programme, along with full counselling of the patient as to the risks of progression.

Cambridge Prognostic Group (CPG)	**Criteria**				
1	Gleason 3+3	*AND*	PSA <10ng/ml	*AND*	T1-T2
2	Gleason 3+4	*OR*	PSA 10-20ng/ml	*AND*	T1-T2
3	Gleason 3+4	*AND*	PSA 10-20ng/ml	*AND*	T1-T2
	OR				
	Gleason 4+3	*AND*	Any PSA		
			AND		
4	Gleason 4+4	*OR*	PSA >20ng/ml	*OR*	T3
5	Any combination of G4+4, PSA >20ng/ml or T3				
	OR				
	Gleason 9-10				
	OR				
	T4				

Available data from a number of series suggest clear dichotomy with intermediate risk/CPG 2 patients in relation to certain risk factors. NCCN/ASCO guidelines suggest a number of risk factors for intermediate risk disease, which are broadly mirrored by those suggested in the EAU guidelines .

Number of cores was suggested in the past to be a predictor of progression, though increased use of targeted biopsies makes the significance of total core numbers involved harder to assess. Instead, more weight can be placed on the Greatest Percentage Core involvement (GPC), with more than 50% of a single core involved being a risk factor for progression. Other risk factors are listed below. If there are less than 2 risk factors observed, AS can be recommended for intermediate risk disease.

If two or more risk factors are present, then the man should be counselled as to the higher risk of disease progression before entering into an AS programme. It is suggested that these unfavourable intermediate risk patients should be discussed at the sMDT before being offered AS as the MDT may feel that the standard AS protocol requires adaptation to take into account the specific risks of that individual (for example, early f/up MRI, different approach for confirmatory biopsies etc.).

NICE NG131 risk stratification states that T2c disease should be considered high risk (and therefore not suitable for AS), though the increased use of imaging and TP biopsies may well increase the amount of T2c cases. It is therefore suggested that low volume T2c patients (on biopsy +/- imaging) should be considered for AS in the absence of other risk factors.

Patients with unfavourable characteristics or in Cambridge Prognostoc Group 3 should be strongly counselled as the risk of progression before entering into an Active Surveillance programme. Written information should be provided along with full documentation in the clinical record.

Intermediate Risk Factors	
Family History*	Prostate Cancer
Race	Afro-Caribbean/African
mpMRI Findings	PSAD >0.15ng/ml/ml PIRAD 5 lesion
Biopsy Findings	>50% GPC >10% pattern 4 component
Patients with family history of genetic predisposition (e.g. BRCA, Lynch etc.) should be counselled towards Active treatment due to high risk of progression	

Confirmatory Biopsies.

Reported series have demonstrated disease upgrades consistently in 20-30% of men on confirmatory biopsies at 6-12 months. It is not clear if this represents true disease progression, sampling issues or a combination of both. However if confirmatory biopsies are performed, both systematic and targeted biopsies (where there is an mpMRI abnormality) should be performed. Up to 10% of lesions can be missed on a targeted approach alone, whereas confirmatory biopsies with a combined targeted and systematic approach yielded an upgrade of 27%. Similarly, 12% of men with a ‘normal’ mpMRI (i.e. PIRAD 2) had an upgrade on systematic biopsies.

It is therefore suggested that Confirmatory biopsies should still be performed at 12 months, with targeted biopsies when appropriate in addition to systematic biopsies. There may be occasions

when a confirmatory biopsy can be avoided, such as in low risk disease with a normal MRI and no unfavourable risk factors. However, confirmatory biopsies should always be considered for unfavourable intermediate risk disease or CPG 3 patients.

Surveillance Investigations

Published series have demonstrated disease progression up to 10 years into AS programmes, so further investigations should be continued. However, there is an increasing shift with towards replacing repeat biopsies with serial mpMRI. Again, within region there has been significant variation in frequency of mpMRI in this context.

On the basis of published series, the current guidelines recommended; *Repeat biopsies at year 4, 7, 10, then every 5 years until moved to WW.* The available literature supports the need for ongoing assessments (rather than reliance on PSA and DRE alone), though in low risk patients mpMRI can be used in place of repeat biopsies. Due to the favorable prognosis associated with negative confirmatory biopsies, repeat biopsies can also be deferred in this situation (i.e. if the initial confirmatory biopsies are negative for a low risk patient).

Confirmatory biopsies should include systematic as well as targeted biopsies due to high reported rates of lesions not identified on targeted biopsies alone.

Patients with a suspected familial component for their prostate cancer can be referred to the newly launched Familial Prostate Cancer Clinic (from early April 2021) which will run alternate weeks at The Christie.

Suggested Follow-up Protocols

Low risk/CPG 1 (PSA <10 and Gleason 6 and T2)	
3, 6, 9 months	PSA
12 months post diagnosis	DRE
12-18 months	mpMRI
Every 6 months until AS moved to WW	PSA and DRE*
If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or re-biopsy	

Favourable Intermediate risk/CPG 2 (i.e. less than two risk factors)	
3, 6, 9 months	PSA
9-12 months	mpMRI (if not done pre-diagnosis)
12 months post diagnosis	MRI will be required pre-confirmatory biopsy at the 12 month post-diagnosis point.
Every 6 months until AS moved to WW	PSA and DRE*
Year 4, 7, 10 after enrolment	Diagnostic Reassessment (mpMRI +/- Bx, depending on risk)
Year 10+	Diagnostic Reassessment (mpMRI +/- Bx, depending on risk) every 5 years until moved to WW

Unfavourable intermediate risk/CPG 2 (i.e. two or more risk factors) or CPG 3 in selected circumstances

- Case reviewed at MDT to confirm imaging, histology and decision
- F/up plan based on intermediate (favourable) though may be modified with earlier investigations if specific concerns (e.g. concerns a targeted lesion may have been missed, equivocal histology etc.)

3, 6, 9 months	PSA
9-12 months	mpMRI (if not done pre-diagnosis)
12 months post diagnosis	MRI will be required pre-confirmatory biopsy at the 12 month post-diagnosis point.
Every 6 months until AS moved to WW	PSA and DRE*
Year 4, 7, 10 after enrolment	Diagnostic Reassessment (mpMRI +/- Bx, depending on risk)
Year 10+	Diagnostic Reassessment (mpMRI +/- Bx, depending on risk) every 5 years until moved to WW

Reasons for intervention

- At any point during a surveillance programme, the patient has the right to change their mind and reconsider active treatment. Patients should be fully counselled and should not be treated until a fully informed decision has been reached.

- Active surveillance can be converted to watchful waiting (i.e. PSA and clinical monitoring alone with a view to deferred hormone manipulation). This should be considered when a patients life expectancy is predicted to be less than 10 years.

- PSA change (including a doubling time of <3 years) has a weak link with grade progression and so should trigger further investigations rather than treatment. However, treatment should be considered if PSA risk group changes (i.e. PSA rising above 10ng/ml in low risk/CPG 1 disease or 20 ng/ml in intermediate/CPG 2 disease). If there are two successive rises in PSA though, clinical review is mandated.

- MRI changes may signify progression, though caution should be applied before a decision to treat is made on imaging alone. In the absence of other signs of progression, repeat biopsies are recommended to further assess the need for intervention. Clinical review is required if progression is reported on surveillance MRIs.

- An increase in Gleason grade on repeat biopsies or an increase in volume to >50% TPC is an indication for treatment. Clinical judgement should be used if upgraded biopsies were from an area targeted for the first time as this may represent variance in biopsy techniques rather than true progression.

Summary

Inclusion Criteria

- NICE NG131 low risk or CPG 1 patients offered AS as preferred treatment option. Can be protocolised at MDT review
- NICE NG131 intermediate risk with one or fewer unfavourable characteristics or CPG 2 patients offered AS as a treatment option, though should be seen in joint Uro-Oncology clinic to discussion all treatment options. Can be protocolised at MDT review.
- NICE NG131 intermediate risk with two or more unfavourable characteristics or CPG 3 should be encouraged to undergoing radical treatment. AS can be considered but only after discussion at MDT and with full counselling as to risks of progression.
- NICE NG131 high risk or CPG 4-5 patients should not be offered AS.

Protocol

- First year; PSA on 3 monthly basis. 6 monthly thereafter.
- mpMRI should be arranged at 9-12 months following diagnosis. May be avoided if low-risk/CPG 1 and transperineal biopsies at diagnosis
- Confirmatory biopsies (systematic +/- targeted if applicable) at 12 months. May be avoided IF low-risk/CPG 1 and transperineal biopsies at diagnosis.
- Intermediate risk/CPG 2-3 patients require serial re-investigation on a three-year cycle as a minimum with mp MRI +/- as indicated. There should be a low threshold for repeat biopsies in intermediate risk patients with 2 or more risk factors or CPG 3.
- AS should continue until no longer suitable for radical therapy

Reason for Intervention

- Patients should have the option of electing to have treatment at any point provided full counselling has taken place.
- Rising PSA alone not a trigger for treatment, though indicates need for further investigation (mpMRI +/- biopsy). Treatment can be considered if risk group changes through rise.
- MRI changes may indicate a need for treatment, though clinical judgement should be applied, especially in absence of other symptoms.
- Increase in tumour grade or volume is an indicator of need for invention.