

## HANDLING - POST NEOADJUVANT SKIN CANCER SPECIMENS

### DOCUMENT CREATED BY:

A/Prof Nima Mesbah Ardakani, Team Lead Dermatopathology, PathWest Laboratory Medicine

### INTRODUCTION

While the initial proposal from International Neoadjuvant Melanoma Consortium (INMC) recommended an extensive sampling of post neoadjuvant specimens to increase the accuracy of the assessment of response (1), recent studies including a large number of specimens analysed from multiple clinical trials have shown that it is possible to reduce the amount of tumour bed examined with no significant compromise in accurate determination of response and percentage of viable tumour (2).

Therefore, the original INMC recommendations have been re-evaluated and updated following adaptation and validation through numerous clinical trials, and new recommendations has been developed via expert consensus as part of a new group “Society for Immunotherapy of Cancer (SITC)”, to provide a pan-tumour/pan-therapy grossing protocol and scoring system for assessment and reporting of treatment response. The new guidelines are highly reproducible across pathologists for assessing of percentage of residual viable tumour (%RVT) in primary tumours, lymph nodes, and distant metastases (3).

These new guidelines are applicable to twelve tumour types; however, the current document is prepared based on the new data generated from a number of clinical trials and updated SITC/INMC recommendations, specifically for grossing and reporting of skin cancer specimens including melanoma, squamous cell carcinoma (SCC) and Merkel cell carcinoma (MCC) by PathWest Dermatopathology.

The purpose of this document is to provide a method for standardised grossing and material submission of post-neoadjuvant skin cancer specimens.

### CLINICAL INFORMATION TO BE PROVIDED TO PATHOLOGY LAB WITH SURGICAL SPECIMENS

Specimen handling and reporting from patients treated in the neoadjuvant setting requires additional considerations beyond most current standardised protocols such as the Royal College of Pathologists Australasia (RCPA) or College of American Pathologists (CAP) guidelines.

*It is imperative that the pathology team be made aware that the patient received neoadjuvant systemic therapy at the time of pathology specimen handling and tissue submission. Failure to do so may result in unsalvageable inappropriate macroscopic assessment, tissue submission and inaccurate evaluation of treatment response.*

**Important note for pathologists and laboratory staff:**

*Neoadjuvant therapy becoming the standard of care for metastatic and locally advanced melanoma and increasing applied to SCC and MCC; therefore, it is prudent to assume that resection specimens (typically large skin & soft tissue resection or lymph nodes) for such tumours are post-neoadjuvant and if not clearly stated on the request form, an attempt must be made to inquiry to the clinical team before approaching the specimen.*

**GROSS EXAMINATION AND SPECIMEN HANDLING**

Resection specimens from patients treated with neoadjuvant therapy may include the primary tumour ± regional lymph nodes, a lymphadenectomy specimen only (as in melanoma), or sometimes regional soft tissue deposits or distant metastases. The largest dimension of the tumour directs the amount of sampling for both the primary tumour and lymphadenectomy specimens.

*Notably, patients enrolled in certain clinical trials may have different specimen handling and tissue submission specifications, including additional grossing requirements. In such instances, this guideline should be supplemented with trial specific instructions.*

**For routine cases, the specimen should be handled according to general skin grossing and tissue submission protocols (PathWest, FastTrack, Clinical Staff Portals) and tumour specific RCPA protocols.**

- This includes requisite sections for the assessment of margin status, the submission of lymph nodes, assessment for potential extra-nodal extension, and other parameters that support standard American Joint Committee on Cancer (AJCC) classification and staging.
- The specimen should be sectioned to identify the tumour/tumour bed. Lesions should be measured and recorded in three dimensions.
- The specimen should be photographed and the block selection marked on the photograph.

**After tissue handling per routine pathology staging protocols, additional tissue submission should be performed as described below.**

The tumour/tumour bed submission from primary tumour, lymph nodes, and/or other metastases should include grossly obvious tumour/tumour bed, inclusive of fibrotic, necrotic, and haemorrhagic areas.

**(i) Tissue submission for primary tumour specimens with greatest tumour dimension  $\leq 3$  cm**

Tumour/tumour beds  $\leq 3$  cm should be submitted in their entirety. If lymph nodes are present with the specimen, please refer to section (iii) and (iv) below.

**(ii) Tissue submission for primary tumour specimens with greatest tumour dimension  $> 3$  cm**

In addition to following standard grossing protocols for assessment of margin status, at a minimum, one complete cross-section of tumour/tumour bed from the longest dimension of the tumour should be submitted along with one section/block per every additional 1 cm of the tumour.

- When possible, the interface of tumour with surrounding normal tissue should also be included.
- For tumours that have a plaque-like growth pattern that is not amenable to a representative cross-section along the long axis, it may be necessary to submit the entire tumour. If this will require

an excessive number of blocks (more than ~20 blocks), systematic sampling of every second or third section while ensuring the capture of areas with variable gross appearance is recommended.

- Attention should be paid to describing and sampling any areas of macroscopically different tumour bed. It is important that this is clearly correlated with the specimen photography to avoid errors in calculating percentage viable tumour.

**(iii) Tissue submission for lymphadenectomy specimens with greatest tumour deposit/lymph node dimension  $\leq 3$  cm**

All identified lymph nodes should be sampled in their entirety for histologic evaluation per standard staging protocols. In addition, each tumour deposit  $\leq 3$  cm should be entirely submitted, including any grossly evident extra-nodal extension or matted nodes.

**(iv) Tissue submission for lymphadenectomy specimens with greatest tumour/lymph node dimension  $> 3$  cm**

All identified lymph nodes ( $\leq 3$  cm) should be entirely sampled. In addition, each lymph node with a tumour/tumour bed deposit  $> 3$  cm in size should be submitted similarly to a primary tumour of this size [described in (ii) above]. In brief, at a minimum, one complete cross-section of tumour/tumour bed from the longest dimension should be submitted for embedding along with one section/block per every additional 1 cm of the tumour/lymph node.

**OTHER SAMPLING CONSIDERATION**

- For both primary tumours and lymph nodes, a regular subsampling may be considered for particularly large lesions which may produce a significant number of blocks (i.e.  $> 25$  blocks for a single large deposit/lymph node) or, alternatively, more complete sampling may be dictated by a *specific clinical trial protocol*.
- At the discretion of reporting pathologist, if a representative additional block per centimetre of large tumour deposits/lymph nodes ( $> 3$  cm) showed histological features of response which are significantly different from the longest dimension cross-section, further material could be submitted from the corresponding slice for histological assessment to ensure an accurate assessment of %RVT and response category.

## **SUMMARY OF PATHOLOGY INSTRUCTIONS FOR NEOADJUVANT SAMPLE HANDLING**

- Open and inspect the entire specimen, report dimensions and location of identified masses.
- Submit for histology per standard grossing instructions for the given tumour type.
- Identify the residual tumour/tumour bed (areas of fibrosis, necrosis, and haemorrhage).
- Measure each tumour/tumour bed in three dimensions and record in the gross description.
- If more than one tumour mass is present, measure and sample each as described below, and identify clearly each individual mass in the gross description and in cassettes/slide labelling.
- Include a Summary of Sections and any pertinent information if limited sections were taken or other reasons impacting quality and quantity of the sampling.
- Submit a photograph/sketch diagram with annotations to show where tissue sections taken.

### **For tumours >3 cm:**

- Submit one complete and full cross section of the residual tumour/tumour bed.
- Submit a section from each additional 1 cm of greatest tumour/tumour bed dimension.

### **For tumours ≤3 cm:**

- Section tumour/tumour bed along long axis and submit the entire tumour/tumour bed.
- If no obvious tumour nodule is present (i.e., cases of suspected complete response), any suspicious or fibrotic areas should be entirely submitted for histologic examination.
- If no suspect areas are evident, submit the entire region known to harbor tumour based on diagnostic biopsy and/or radiographic studies.
- If those studies are not available, it may be necessary to submit the entire specimen.

### **For specimens containing lymph nodes:**

- Section and submit tumour/tumour bed areas as described above.
- Identify clearly the precise number of suspected lymph nodes in the gross description and also in cassettes & slide labelling.
- All resected lymph nodes ≤3 cm should be submitted in their entirety. For lymph nodes > 3 cm in size follow the above instruction as for tumours >3 cm. If information is provided on the request form regarding the anatomic location/substation of the lymph nodes, please annotate this information for the corresponding blocks.

**Figure A. Example of grossing protocol applied to a lymphadenectomy specimen with two tumour deposits. One tumour is 5 cm in size and another, smaller deposit is 2 cm in size. A summary of sections is provided.**

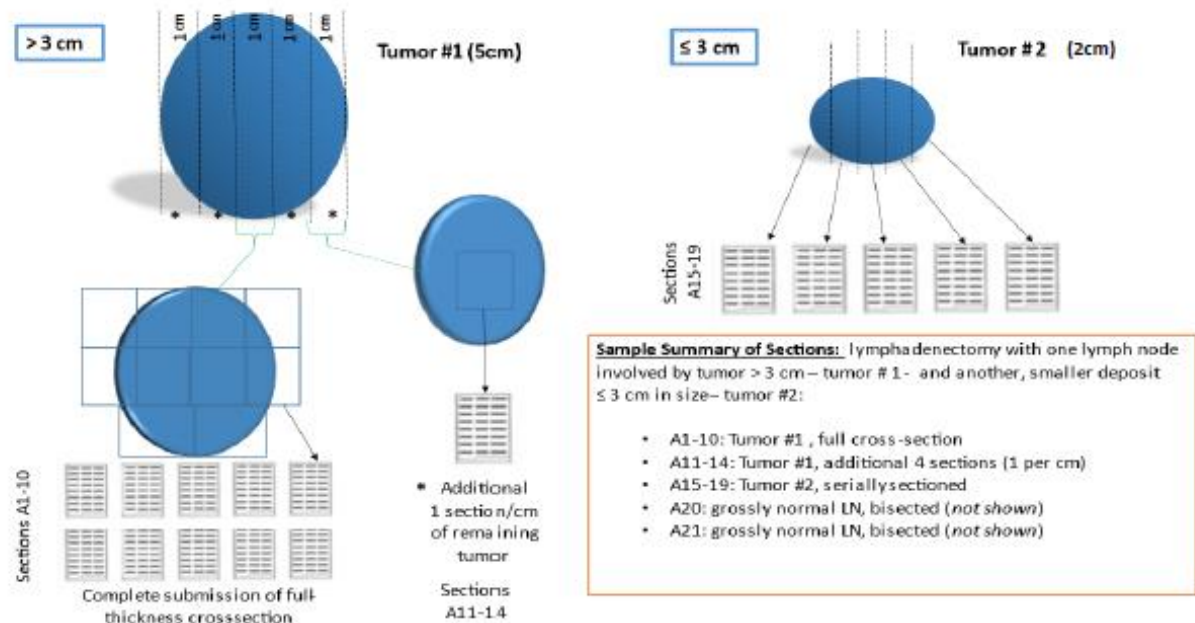
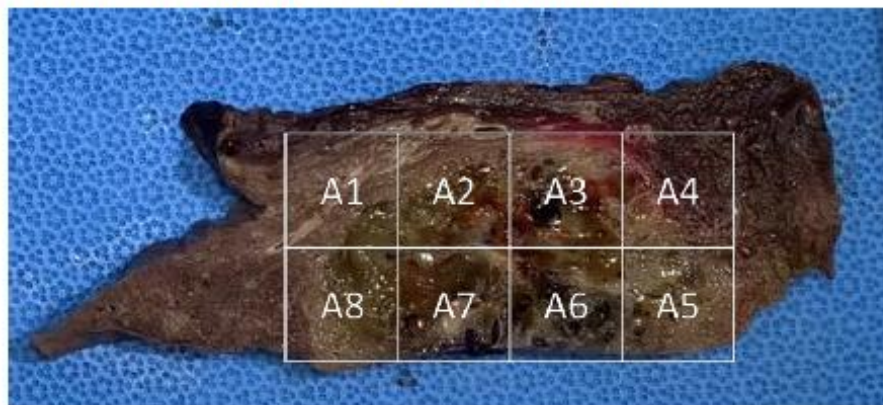


**Figure B. Example gross photograph with cassette/block annotations**



## REFERENCES

1. Tetzlaff MT, Messina JL, Stein JE, Xu X, Amaria RN, Blank CU, et al. Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma. *Ann Oncol.* 2018;29(8):1861-8.
2. Rawson RV, Maher NG, Menzies AM, Lo SN, Mesbah Ardakani N, Jakkett LA, et al. Pathological response calculation assessment remains accurate with reduced tumor bed examination after neoadjuvant immunotherapy in clinically detectable stage III melanoma. *Ann Oncol.* 2026;37(2):206-16.
3. Deutsch JS, Scolyer RA, Burton E, Busam KJ, Chen KY, Cimino-Mathews A, et al. Updated pan-tumor guidelines for neoadjuvant scoring of pathologic response: a joint SITC and INMC effort. *Ann Oncol.* 2026;37(2):141-54.