

REPORTING - POST NEOADJUVANT SKIN CANCER SPECIMENS

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Neoadjuvant systemic immunotherapy has become the standard of care in advanced cutaneous melanoma with clinically detectable metastatic disease and is becoming an option for locally advanced and metastatic cutaneous squamous cell carcinoma, resulting in significant improvement in patients' survival. (1, 2) In addition to improved survival, there are other advantages in neoadjuvant therapy including:

- (i) Providing a unique window to gauge the anti-tumoural efficacy via pathological assessment of the resection specimen
- (ii) Potential to shrink unresectable tumour; less morbid surgery
- (iii) Eradication of clinically occult disease

The foundational purpose of pathological assessment of post-neoadjuvant specimens (including melanoma and SCC) is to assess the pathologic response by calculating the percentage residual viable tumour (%RVT). (3)

%RVT is determined by the proportion of viable tumour after therapy in relation to the largest extent of the tumour before therapy (also nominated as tumour bed) and is calculated using the following formula:

$$\% \text{ residual viable tumor} = \frac{\text{surface area of residual viable tumor}}{\text{surface area of total assessed cross-sectional tumor bed}}.$$

MICROSCOPIC ASSESSMENT OF EXCISED PRIMARY TUMOUR OR CUTANEOUS TUMOUR DEPOSITS

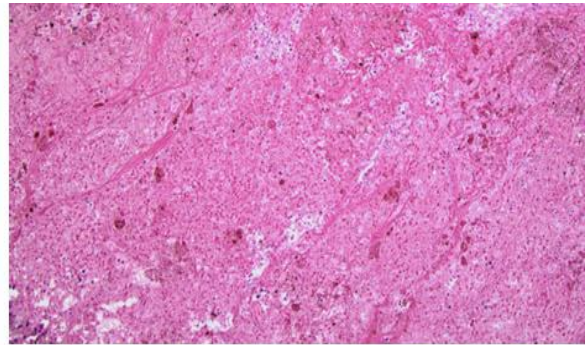
The components that constitute the tumor bed and should be scored include **RVT**, **necrosis**, and **regression** (in the form of immature/inflammatory or mature/hyalinised fibrosis and/or aggregates of melanophages (also known as "tumoural melanosis") in melanoma or keratin/keratin granulomas in SCC). The total percentage surface area(s) of each of the three components is estimated across all slides containing tumour/tumour bed (**Figure 1** illustrates microscopic images exemplifying histologic features of different forms of regression).

- It is recommended that, when possible, pathologists use slide marking pens on glass slides or annotate on digital sections to circle the three tissue classes of RVT, necrosis, and regression. When all slides are marked, it is possible for the pathologist to reliably estimate the %RVT across all slides visually, which obviates the need to perform direct on-slide measurements with a micrometer or image analysis.
- If multiple foci of residual tumour present, these are added and reported together for the calculation of RVT surface area, provided they are located in a single tumour bed (**Figure 2**).

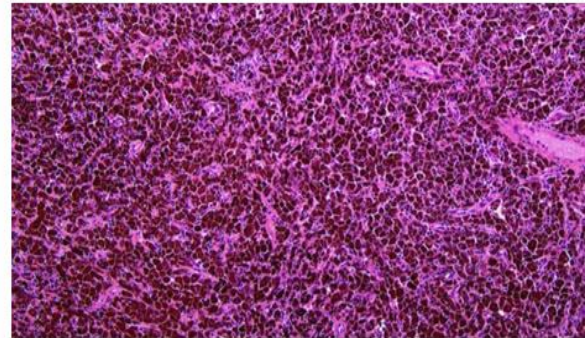
- When multiple separate invasive primary tumours are identified, they should be scored individually for response.
- When estimating the surface area involved by tumour, in situ/non-invasive disease is not included in the calculation.
- Focal “comedonecrosis” should be considered as part of the “viable tumour” surface area, while larger, broad areas of geographic tumour necrosis should be counted in the necrosis category.
- IHC may be used at the pathologist’s discretion in challenging cases to help identifying residual tumour. However, it is not recommended as a reflexive test.
- Routinely generating and examining multiple slide levels from a single block is also not necessary nor recommended.

Figure 1.

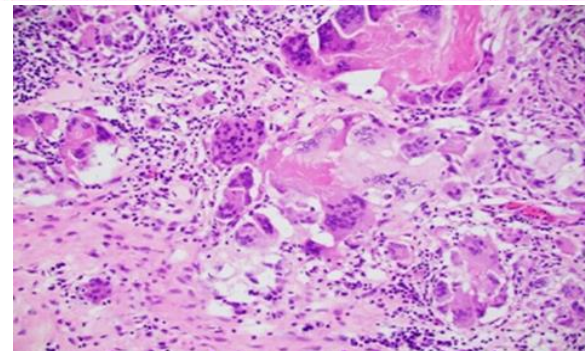
Necrosis



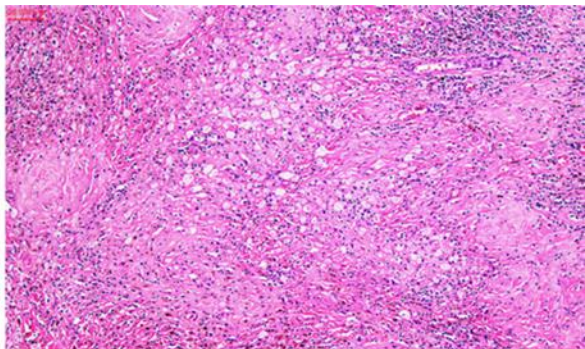
Tumoral melanosis pattern



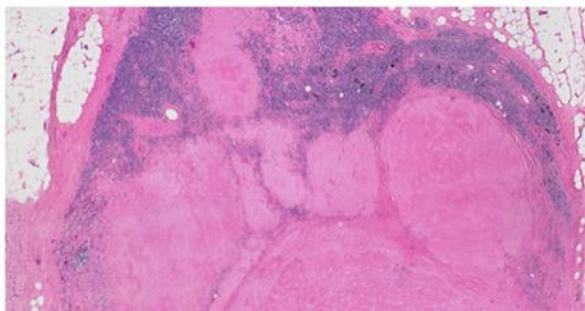
Keratin Granulomas



**Inflamed fibrosis pattern
(immature/proliferative)**



Hyalinise Fibrosis



MICROSCOPIC ASSESSMENT OF EXCISED LYMPH NODES

All lymph nodes in the resection specimen should be examined for features of viable tumour, necrosis, and regression. Similar to the primary tumour, surface area measurements are added across all slides from all lymph nodes in the specimen to generate %RVT, %necrosis, and %regression for the lymph node compartment.

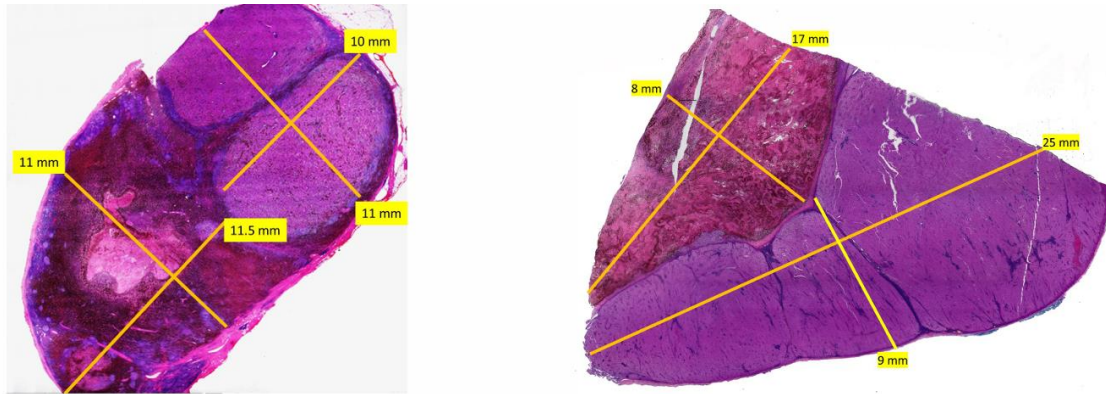
- The histologic features of regression are consistent enough that it is possible to distinguish a normal lymph node that was never involved by a well-established tumor deposit (more than isolated tumor cells in parenchyma or those confined to a subcapsular sinus) from one that was involved and has undergone pathological complete response (pCR).
- Hyalinised granulomas, sinus histiocytosis and anthracotic macrophages must be distinguished from features of regression, as these do not reflect tumor clearance.
- Histologically unremarkable, normal lymph nodes that were never involved by tumour are not included in the surface area calculation for %RVT assessment.
- The %RVT of the lymph node compartment is determined separately from the primary tumour.

ASSESSMENT OF SPECIMENS CONTAINING BOTH PRIMARY TUMOR AND LYMPH NODES

For cases where there is a primary tumour and regional lymph node deposits, it is recommended that %RVT for both are captured and reported as discrete variables, since the relative contribution to clinical outcomes for the %RVT in the primary tumour and %RVT in the lymph node compartment is not yet known.

Such approach will also allow for studies to determine the prognostic significance of mixed responses between anatomic compartments, including the relative significance of residual primary versus metastatic tumor. While the optimal combination is yet to be determined, if a global value (taking into account all tumour deposits at multiple sites, including distant metastases, if present) is provided, it should be:

- Provided in addition to %RVT in each compartment (primary tumor, regional lymph nodes); and
- An aggregate surface area measurement, rather than a strict average of %RVT from the different locations.

Figure 2.

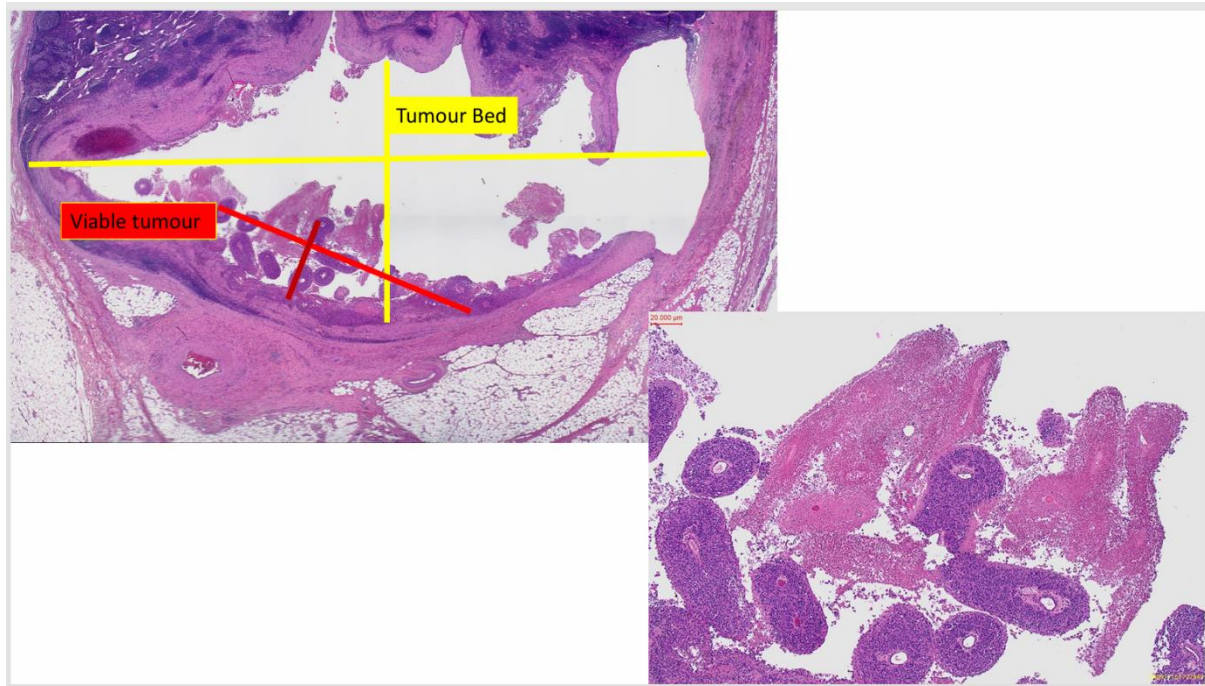
$$25 \times 9 + 11 \times 10 / (25 \times 9) + (17 \times 8) + (11 \times 10) + (11.5 \times 11) = 0.56$$

%viable tumour = 56%

Response category: pNR

Less commonly encountered histological alterations:

- In addition to the typical features (fibrosis and neovascularisation, necrosis, melanophages and keratin with associated granulomas), other features of regression that may be present include *plasma cells, foamy macrophages, lymphocytes and tertiary lymphoid structures (TLSs)* and *cholesterol clefts*. The proportion of each of these features may vary, depending on the phase of regression, with more lymphocytes seen in actively regressing lesions and more macrophages seen in the tumor bed of tumors that have already regressed.
- Another possible finding is the presence of areas of *cystic change or fluid (seroma or blood) accumulation*. There is no specific guideline in the literature outlining how to assess such areas; therefore, it is incumbent up on the pathologist to make a judgmental call based on the circumstances surrounding individual specimens. For example, areas of cystic change/fluid accumulation replacing foci of regression (due to tissue disintegration following necrosis) should be calculated as part of tumour bed; in contrast, a cystic haematoma following a previous surgical procedures/trauma (such as core biopsy) should not be accounted as tumour bed (**Figure 3**).
- In cases where it is possible to distinguish between a *desmoplastic tumor stroma* (which lacks neovascularization and other key components of bona fide regression) and regression bed, the surface area of the tumour stroma should be included in the surface area for viable tumour, rather than as part of the surface area of fibrosis associated with regression.
- In rare circumstances, histologic assessment of a specimen, typically lymph nodes, may reveal an *absence of both viable tumour and evidence of regression* (tumour bed). Such cases should be considered as complete regression (complete pathological response/pCR), after a generous sampling of specimen and meticulous clinicopathological and imaging correlation to ensure that the correct anatomical region/nodal levels have been excised. These cases may represent regression of low volume metastatic disease which may have resulted in minimal/non-identifiable inflammatory response.

Figure 3.

DEFINING PATHOLOGIC RESPONSE AND ASSOCIATED REPORTING RECOMMENDATIONS

- It is recommended that %RVT, %regression (fibrosis, melanophages and keratin/keratin granulomas), and %necrosis are each measured and reported at 10% intervals (0%, followed by rounding to the nearest 10%, 20%, 30%, etc.), except for when %RVT is between 1% and 5%, in which single percentages should be recorded (0%, 1%-5%, 10%, and increasing 10% RVT increments). If any tissue class has a value in the 1%-5% range, the other tissue classes may not have values that are a factor of 10, as the total values of the three tissue classes must sum to 100%.

The rationale for capturing the full spectrum of %RVT is that a continuum of pathologic responses from 0% to 100% may be observed and inversely correlates with improved patient outcomes in many tumour types. (4)

RESPONSE CATEGORIES

- **Pathologic complete response (pCR)**- Complete absence of viable tumour in the treated tumour bed
- **Near-pCR (pnCR)**- $\leq 10\%$ of viable tumour in the treated tumour bed
- **Major pathologic response (MPR)**- Both pCR /near-pCR, thus $\leq 10\%$ of viable tumour in the treated tumour bed
- **Partial pathologic response (pPR)**- $\leq 50\%$, but $>10\%$ of the treated tumour bed is occupied by viable tumour
- **No pathologic response (pNR)**- $>50\%$ of the treated tumour bed is occupied by viable tumour cells

REFERENCES

- (1) Patel SP, Othus M, Chen Y, Wright GP Jr, Yost KJ, et al. Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma. *N Engl J Med*. 2023 Mar 2;388(9):813-823. PMID: 36856617; PMCID: PMC10410527.
- (2) Stratigos AJ, Garbe C, Dessinioti C, Lebbe C, van Akkooi A, et al; EADO, EDF, ESTRO, UEMS, EADV and EORTC. European consensus-based interdisciplinary guideline for invasive cutaneous squamous cell carcinoma: Part 2. Treatment-Update 2023. *Eur J Cancer*. 2023. Epub 2023 Jul 28. PMID: 37708630.
- (3) Rawson RV, Maher NG, Menzies AM, Lo SN, Mesbah Ardakani N, 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 Feb;37(2):206-216. Epub 2025 Nov 1. PMID: 41183783.
- (4) Deutsch JS, Scolyer RA, Burton E, Busam KJ, Chen KY, et al. Updated pan-tumor guidelines for neoadjuvant scoring of pathologic response: a joint SITC and INMC effort. *Ann Oncol*. 2026 Feb;37(2):141-154. Epub 2025 Nov 4. PMID: 41469296.

APPENDIX - SUGGESTED SYNOPTIC REPORTING TEMPLATE:

MICROSCOPIC:

Free text; microscopic description of pertinent histological findings including evidence of presence/absence of tumour/tumour bed and any other significant concurrent histological alterations.

CONCLUSION:

LYMPH NODE

Specimen site:

- Total number of lymph nodes and number of involved lymph nodes (with viable and/or regressed melanoma): \$/\$
- % viable tumour and pathologic response category: \$%; \$.
- % necrosis (optional): \$%
- % Pigmented macrophages/Keratin/keratin granulomas (optional): \$%
- % fibrosis (optional): \$%
- Extracapsular extension: \$

PRIMARY TUMOUR OR CUTANEOUS TUMOUR DEPOSITS

- Total number of lesions with viable and/or regressed melanoma: \$
- Size of the largest viable tumour deposit (mm): \$
- % viable tumour and pathological response category: \$%; \$.
- % necrosis (optional): \$%
- % Pigmented macrophages/keratin/keratin granulomas (optional): \$%
- % fibrosis (optional): \$%