

Pathology That Matters

CRM, Tumor Budding , Treatment Response Grading

From the surgical specimen to clinical decision-making



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The Three Pillars of Prognosis



The Macro (CRM)

Focus

Gross anatomical surgical success.

Impact

Dominant predictor of local recurrence.



The Tissue (TRG)

Focus

Neoadjuvant chemoradiation response.

Impact

Dictates adjuvant chemotherapy utility.



The Cellular (Budding)

Focus

Micro-metastatic vanguard at the invasive front.

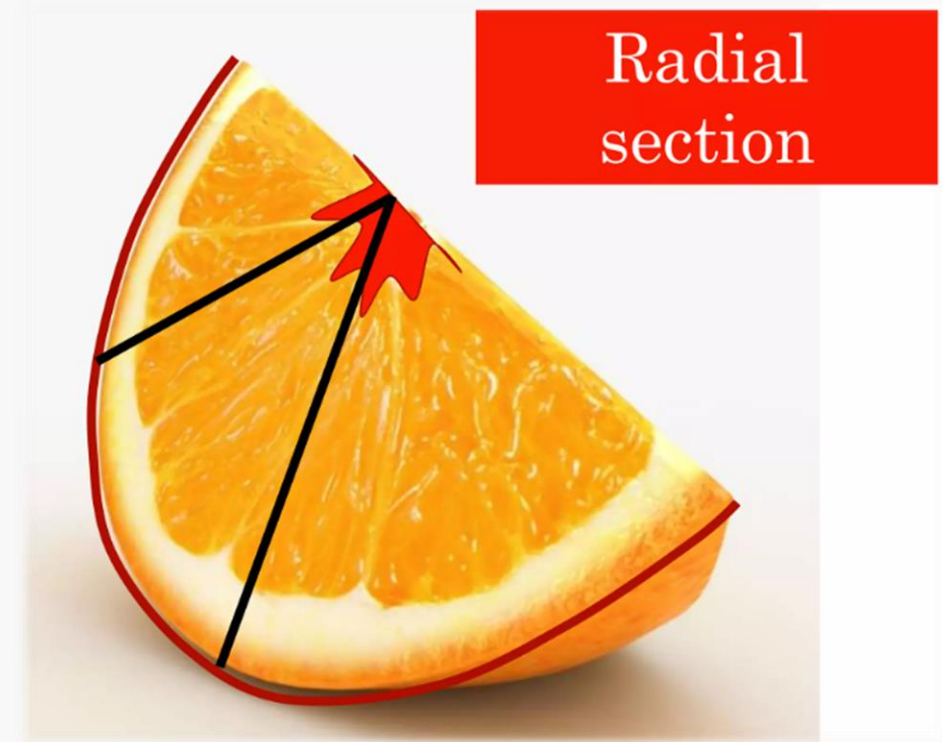
Impact

Predicts lymph node metastasis and stage II recurrence.

Circumferential Resection Margin (CRM)

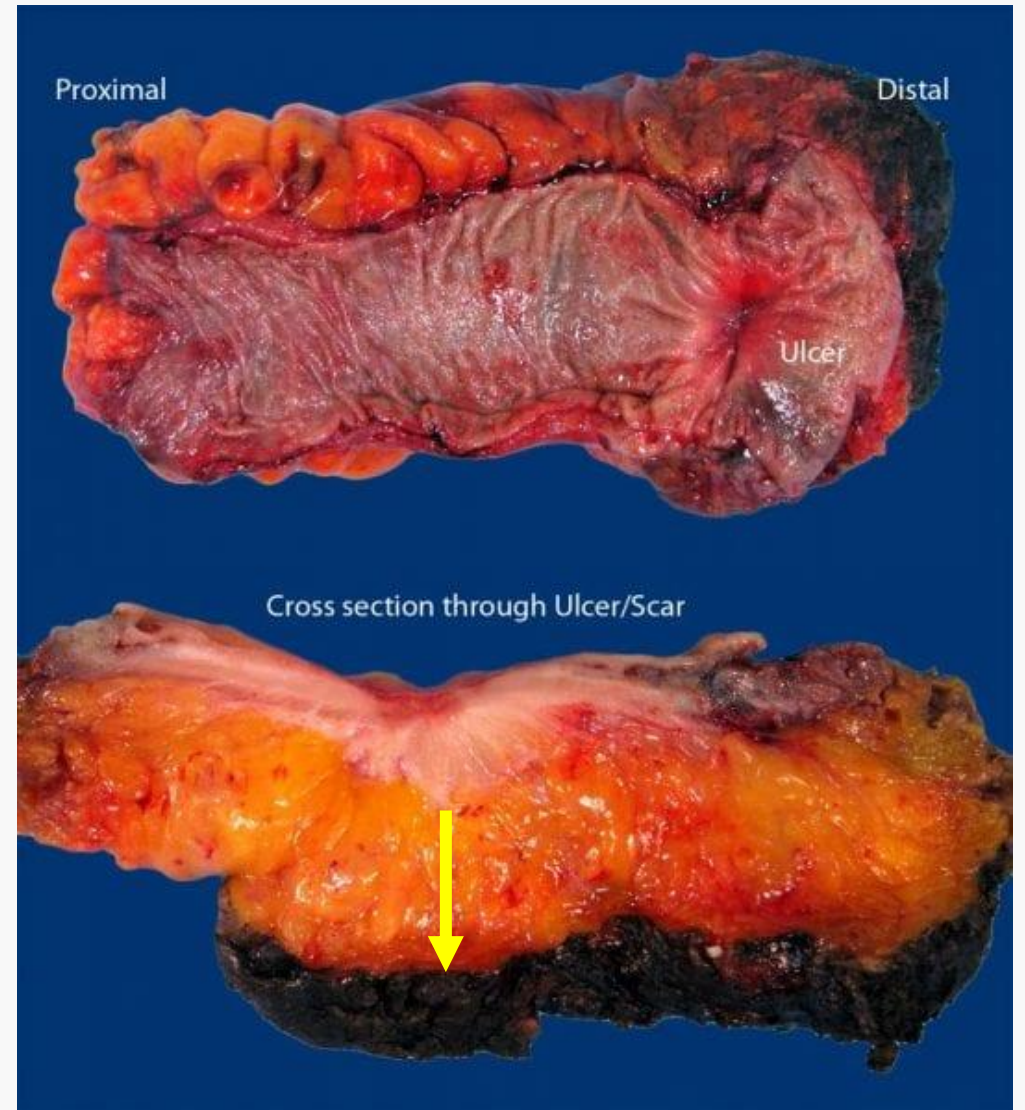


- CRM is the **radial/non-peritonealized soft-tissue margin**, created surgically by dissecting the retroperitoneal / subperitoneal aspect around the rectal tumor
- Since the **lower rectum** is entirely extraperitoneal, the radial margin extends circumferentially, referred to as the **circumferential radial margin**.
- CRM involvement in the rectum carries a high risk of local recurrence and 90% mortality rate.



Circumferential Resection Margin (CRM)

- Unlike the proximal and distal margins, CRM represents the **radial clearance** around the tumor.
- CRM: The measurement of the distance from the deepest extent of the tumor/ulcer to the inked **radial margin** - **MUST** be included in the gross description.
- Requires fresh specimen handling, proper orientation, inking, skilled dissection, accurate measurement.





CRM: Measure; Don't Just Describe

The pathologist should identify the **closest distance between tumor and the inked circumferential margin**.

Reporting as:

CRM: uninvolved; minimum clearance = 3 mm

is much more informative than:

CRM: negative



CRM: The 1-mm Rule

A CRM of ≤ 1 mm has been considered an **involved/high-risk margin**. (*Quirke et al., 1986*)

Quirke P, et al. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet. 1986 Nov 1;2(8514):996-9. doi: 10.1016/s0140-6736(86)92612-7. PMID: 2430152.



Positive CRM $\leq 1\text{mm}$

Direct Extension vs. Intranodal Spread

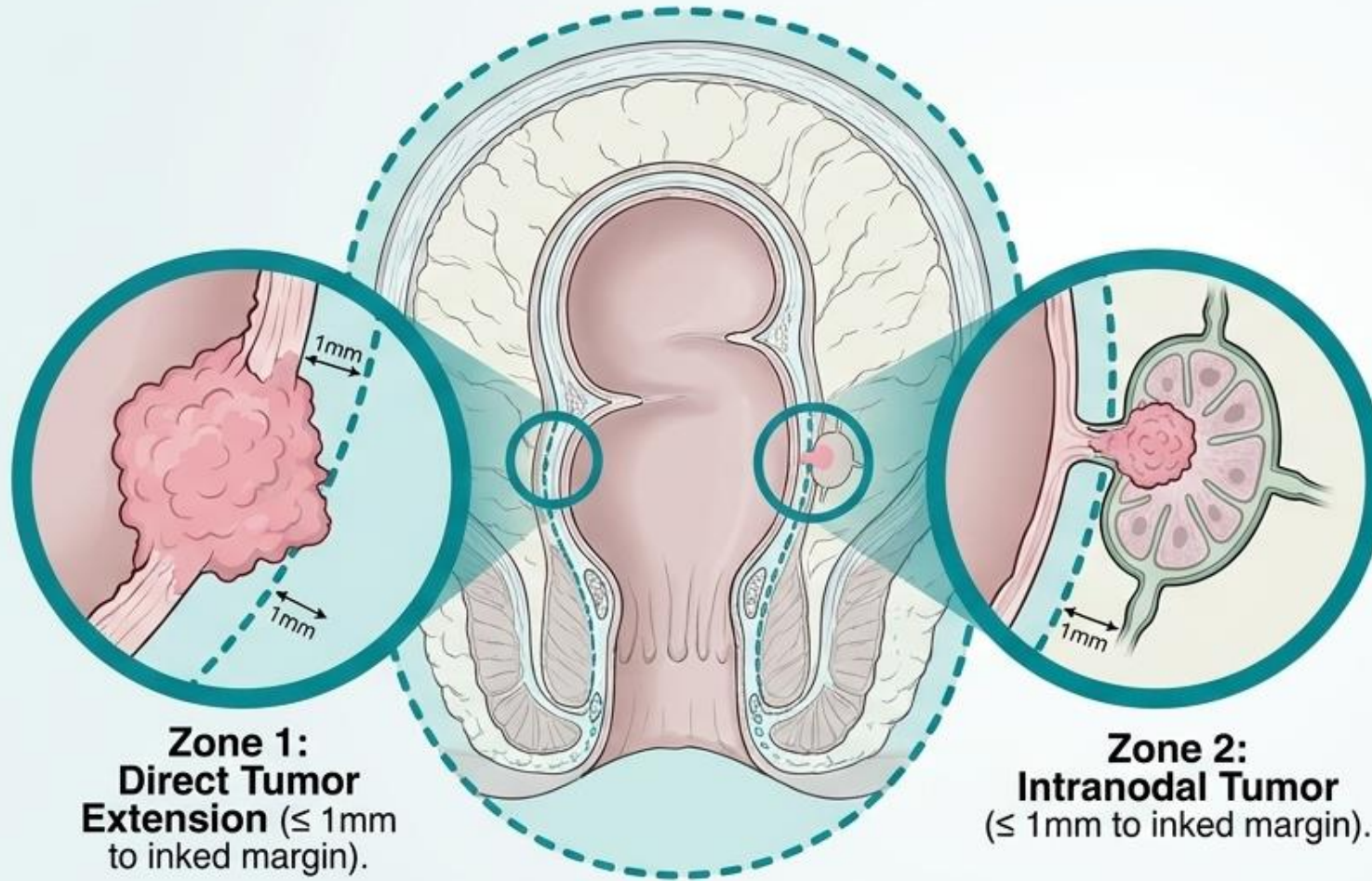
Direct Extension (Direct Tumor Spread):

- Continuous growth of the primary tumor through the rectal wall and into or beyond the mesorectal fascia (within $\leq 1\text{ mm}$).
- Prognosis: A higher risk of local recurrence and lower overall survival because it represents aggressive, infiltrative local tumor growth.

Intranodal Spread (Involved Lymph Node at the Margin):

- CRM positivity caused strictly by a metastatic tumor deposit residing inside a lymph node that sits at or near the radial resection margin.
- Prognosis: Lower risk of local recurrence and significantly better overall survival compared to direct muscle/fat invasion by the primary tumor.

The 1-mm Rule and the Anatomy of a Positive Margin



The Clinical Definition

- **The Absolute Metric:** CRM is positive if the tumor is $\leq 1\text{mm}$ from the inked transected margin.
- **The Nuance:** A positive CRM includes both direct extension and intranodal tumor.
- **Surgical Context:** If positivity is solely based on intranodal tumor, pathologists must state this, as studies show it is associated with lower local recurrence rates than direct extension.



OPINION

Reconsidering the 1 mm rule: Contextualising R1 margin status in rectal cancer

[J. D. Mason](#), [K. Naidu](#), [J. Tiernan](#), [N. P. West](#), [C. Cunningham](#)  on behalf of
[The Association of Coloproctology of Great Britain & Ireland](#)

First published: 25 February 2026 | <https://doi.org/10.1111/codi.70414> |

 [VIEW METRICS](#)

Report the actual distance
Let the MDT interpret it in clinical context

Meaningful CRM Requires Pristine Surgical Technique



Complete

Intact, bulky mesorectum. Smooth surface, no defects deeper than 5mm. No coning.



Nearly Complete

Moderate bulk. Irregular surface with defects >5mm, but muscularis propria is NOT exposed.



Incomplete

Little bulk. Major defects extending down to visible muscularis propria. Highly irregular circumferential margin.

Surgical technique + specimen quality + pathological assessment = Meaningful CRM.
Poor TME quality directly increases the likelihood of an inadequate CRM and local recurrence.



CRM Is a Surgical–Pathological Parameter

CRM assessment begins before the specimen reaches the microscope



Surgeon

- Performs appropriate surgical plane dissection
- Preserves the mesorectal envelope
- Avoids unnecessary disruption
- Provides orientation



Pathologist

- Assesses specimen integrity
- Identifies the radial margin
- Ink the CRM
- Samples the closest area
- Measures the minimum clearance



**Surgical technique +
specimen quality +
pathological assessment
=
Meaningful CRM**



TUMOR BUDDING

Tumor budding is defined as: **Single tumor cells or small clusters of up to four tumor cells at the invasive front.**

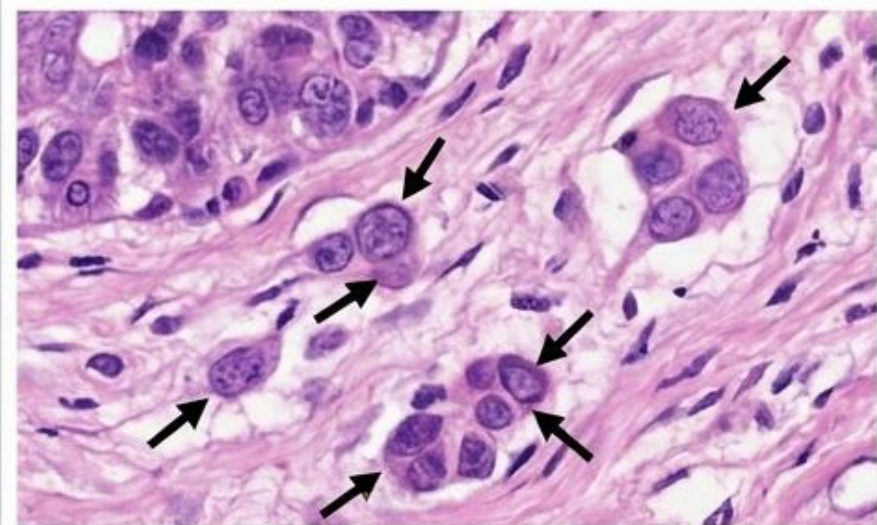
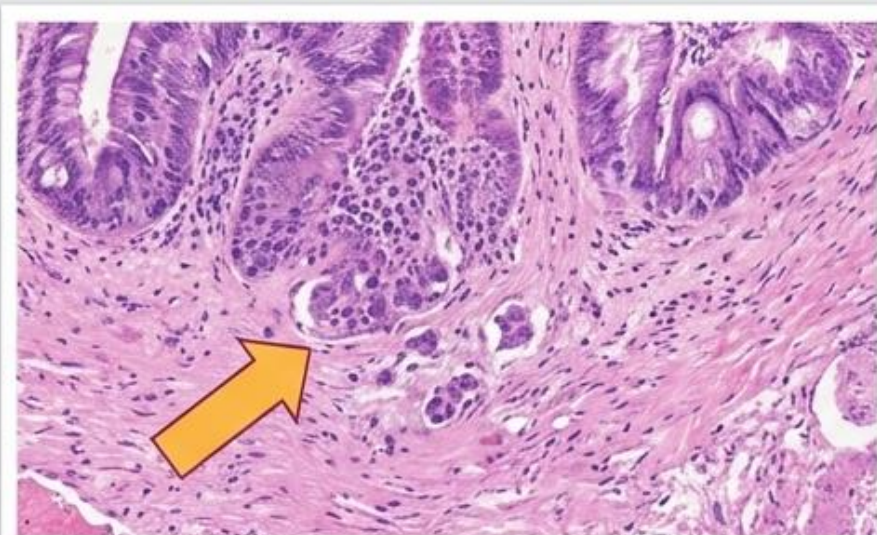
It represents a morphological feature of tumor invasion and is associated with aggressive tumor behavior.

Independent prognostic factor in colorectal cancer:

- Lymph-node metastasis
- Recurrence
- Poorer survival
- More aggressive tumor behavior

The **ITBCC consensus** recommends that tumor budding be considered together with other clinicopathological factors in multidisciplinary risk assessment

Tumor Budding: Identifying the Metastatic Vanguard



Definition:

- A “Tumor Bud” is strictly defined as an isolated single cancer cell, or a cluster of up to 4 cancer cells, at the invasive tumor front. (Cite: ITBCC 2016 Guidelines).

Biological Mechanism:

It represents the morphological manifestation of epithelial-mesenchymal transition (EMT)—the tumor actively preparing to metastasize.

Diagnostic Caveat:

Only reported in non-mucinous, non-signet-ring areas. It is NOT assessed in cancers resected after neoadjuvant therapy.



Biological Distinction: Budding vs. Grade

These parameters provide entirely different biological information and are not interchangeable.

Tumor Grade	Tumor Budding
• Question Answered: “How much gland formation does the primary tumor show?” • Focus: Overall architectural differentiation of the tumor mass. • Utility: General prognostic indicator.	• Question Answered: “How is the tumor behaving right now at its invasive front?” • Focus: Active cellular detachment and motility (EMT). • Utility: Specific predictor of micro-metastasis and lymph node involvement. (Cite: Lugli A, et al. Virchows Arch. 2021).



Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016

Alessandro Lugli^{1,22}, Richard Kirsch^{2,22}, Yoichi Ajioka³, Fred Bosman⁴, Gieri Cathomas⁵, Heather Dawson¹, Hala El Zimaity⁶, Jean-François Fléjou⁷, Tine Plato Hansen⁸, Arndt Hartmann⁹, Sanjay Kakar¹⁰, Cord Langner¹¹, Iris Nagtegaal¹², Giacomo Puppa¹³, Robert Riddell², Ari Ristimäki¹⁴, Kieran Sheahan¹⁵, Thomas Smyrk¹⁶, Kenichi Sugihara¹⁷, Benoît Terris¹⁸, Hideki Ueno¹⁹, Michael Vieth²⁰, Inti Zlobec¹ and Phil Quirke²¹

Crucial Diagnostic Caveat:

- Do not report in **mucinous/signet-ring areas**
- Never assess **post-neoadjuvant therapy**

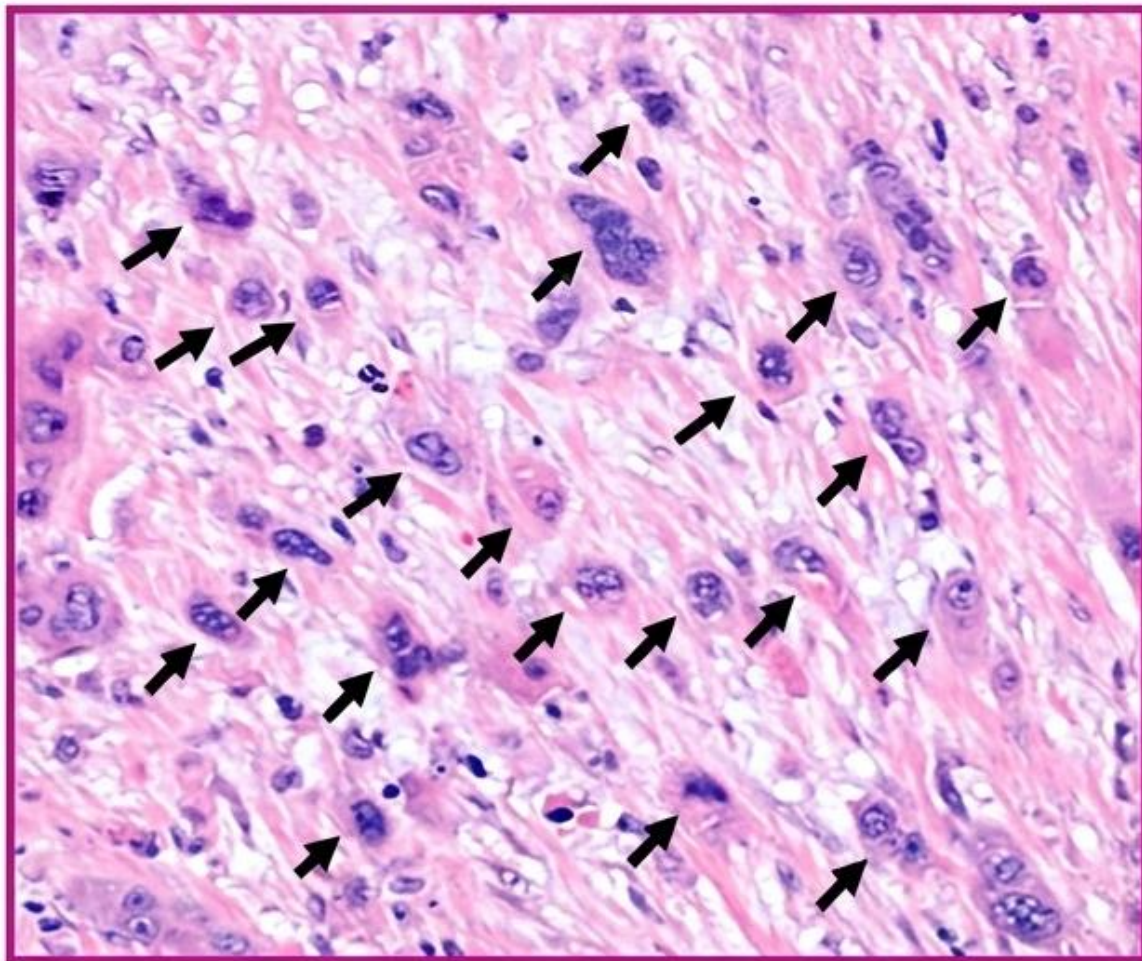


How Is Tumor Budding Assessed?

The **ITBCC** recommends:

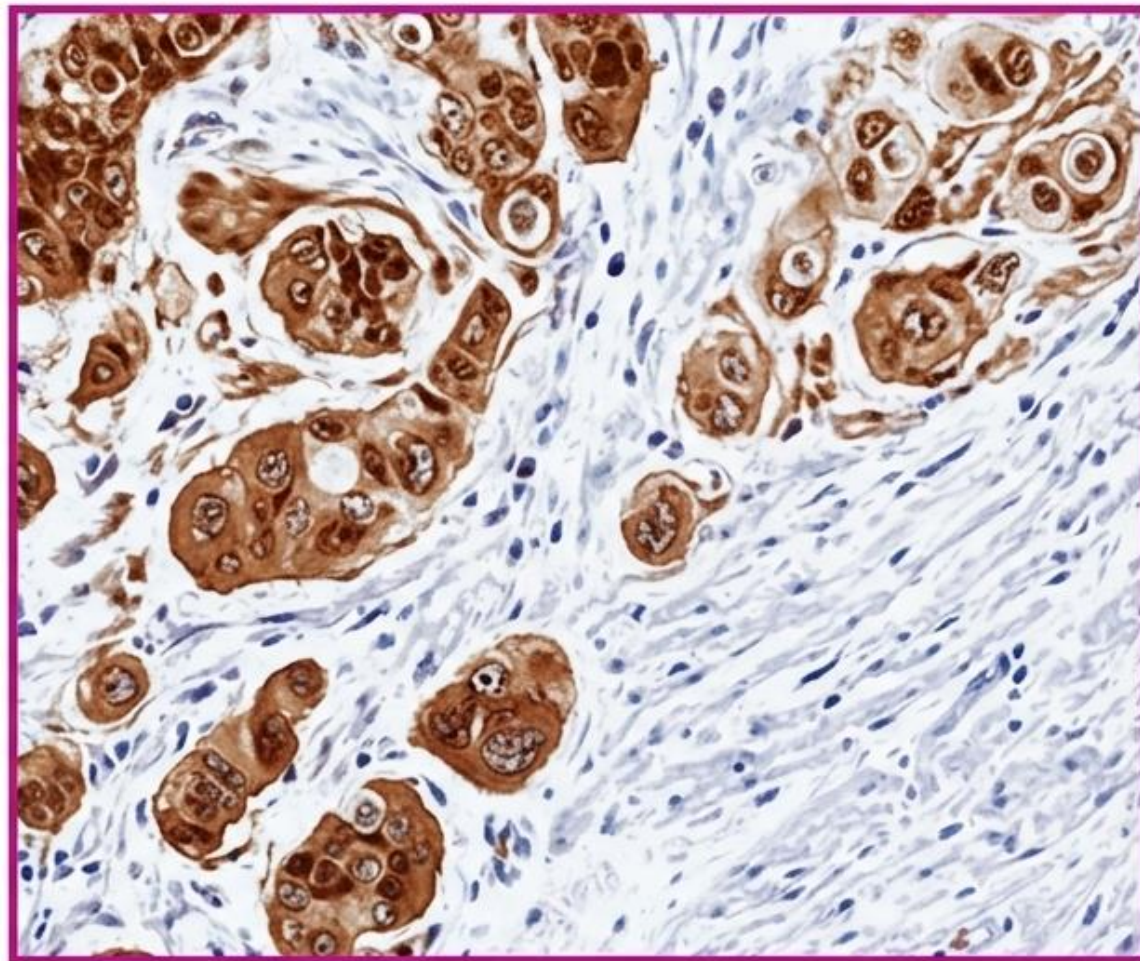
- Assessment on H&E
- Identification of the invasive front
- Selection of the area with the **highest density of buds**
- Counting within a standardized field of **0.785 mm²**
- Reporting the actual bud count
- Assigning a three-tier grade (**ITBCC grading**)
 - **Bd1 — Low**
 - **Bd2 — Intermediate**
 - **Bd3 — High**

Visualizing the Vanguard: The Role of Pankeratin IHC



Left Panel (H&E Stain)

At scanning power, clues include an infiltrating growth pattern, marked irregularity at the invasive front, and a blurring interface. However, intense peritumoral inflammation can obscure accurate budding counts.



Right Panel (Pankeratin IHC Stain)

Pankeratin immunohistochemistry allows for immediate, high-contrast visualization of epithelial tumor buds against the stromal background, significantly improving inter-observer agreement.

Quantifying Budding Risk: The 0.785 mm² Hotspot Protocol



Risk Dashboard

Low Risk (Bd1)

0-4 buds per 0.785 mm²

Intermediate Risk (Bd2)

5-9 buds per 0.785 mm²

High Risk (Bd3)

10 or more buds per 0.785 mm²

Surgical Implications

In pT1 Malignant Polyps

Bd2 and **Bd3** are independent risk factors for hidden lymph node metastasis, often prompting radical surgical resection over endoscopic management.

In Stage II CRC (pT3/T4 N0)

Bd3 is an independent predictor of recurrence and mortality. It identifies high-risk patients who may require adjuvant therapy despite negative nodes.

Tumor Budding: What Should the Surgeon Take From It?

- Tumor budding is **not usually a stand-alone determinant of the surgical procedure.**
- It should be interpreted with:
 - TNM stage
 - Tumor grade
 - Lymphovascular invasion
 - Perineural invasion
 - Lymph-node status
 - Histologic subtype
 - Molecular characteristics

Tumor budding adds information about tumor biology beyond TNM staging.



Case Scenario

Two patients:

Patient A: Stage II colorectal carcinoma
Low tumor budding

Patient B: Stage II colorectal carcinoma
High tumor budding

Same TNM stage.

Do they necessarily have the same risk?

Answer

- Not necessarily.
- Tumor budding is an independent prognostic parameter and may identify patients with higher-risk disease, particularly in stage II colorectal cancer.





TREATMENT RESPONSE

What Is Tumor Regression Grade?

Tumor regression grading evaluates the proportion of:

Residual viable tumor relative to **Treatment-induced fibrosis / regression**.

Several systems have been developed, including:

- Mandard
- Dworak
- AJCC/CAP-type approaches
- Ryan system

These systems are not identical, so the specific system used by the laboratory should be clearly stated.



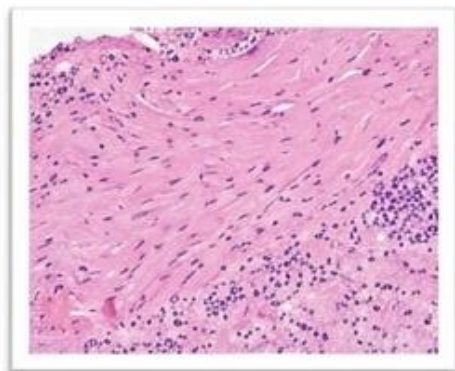
Pathologic complete response (pCR)

- No residual viable carcinoma is identified in the primary tumor bed, with appropriate assessment of regional lymph nodes.
- **Why is this important?** pCR is associated with favorable outcomes.
- A systematic review and meta-analysis of **4,875 patients** found that patients achieving pCR had significantly better overall survival, while non-responding tumors had significantly worse outcomes.
- **But:**

pCR does not mean that the patient requires no follow-up.



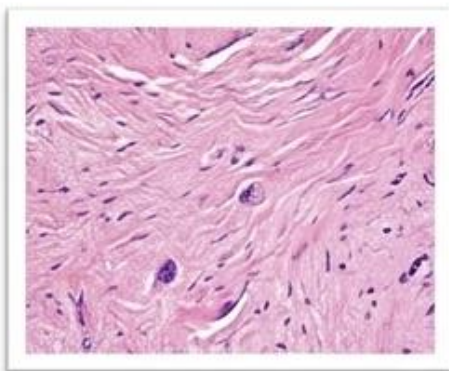
Treatment Response Exists on a Spectrum



TRG 0

(Complete Response)

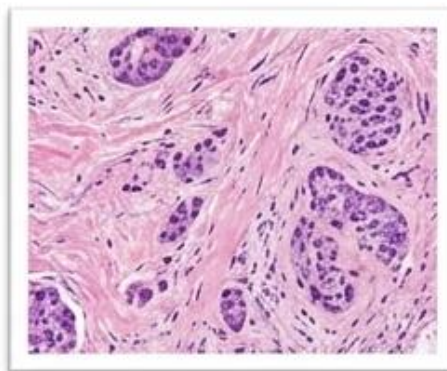
No viable cancer cells. Pure fibroinflammatory tissue or acellular mucin. (Cite: Pathologic Complete Response (pCR)).



TRG 1

(Near Complete)

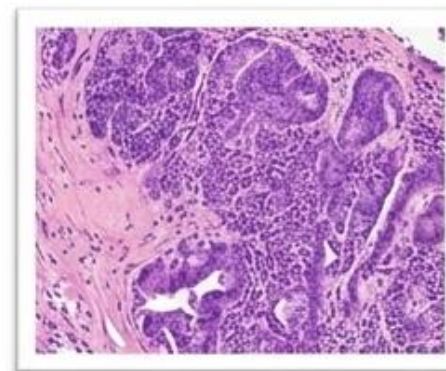
Abundant fibrosis with only rare, scattered single tumor cells.



TRG 2

(Partial Response)

Residual cancer cells easily identified, but fibrosis predominates.



TRG 3

(Poor Response)

Minimal to no tumor kill. Extensive residual adenocarcinoma outgrowing fibrosis.

The pathologist must distinguish treatment effect (fibrosis/necrosis) from residual viable tumor. Tumor bed size does NOT equal viable tumor burden.



The TRG Translation Engine: Navigating Grading Systems

Biological Response	Mandard	Dworak	AJCC/CAP
Complete Response	1	4	0
Near Complete	2	3	1
Partial Response	3	2	2
Poor Response	4/5	0/1	3

Why AJCC/CAP is the Recommended Standard.

Unlike 5-tier systems which clump heterogeneous responses together, AJCC cleanly divides the intermediate zone (TRG 1 vs TRG 2). This improves **interobserver reproducibility** and perfectly aligns with survival divergence.



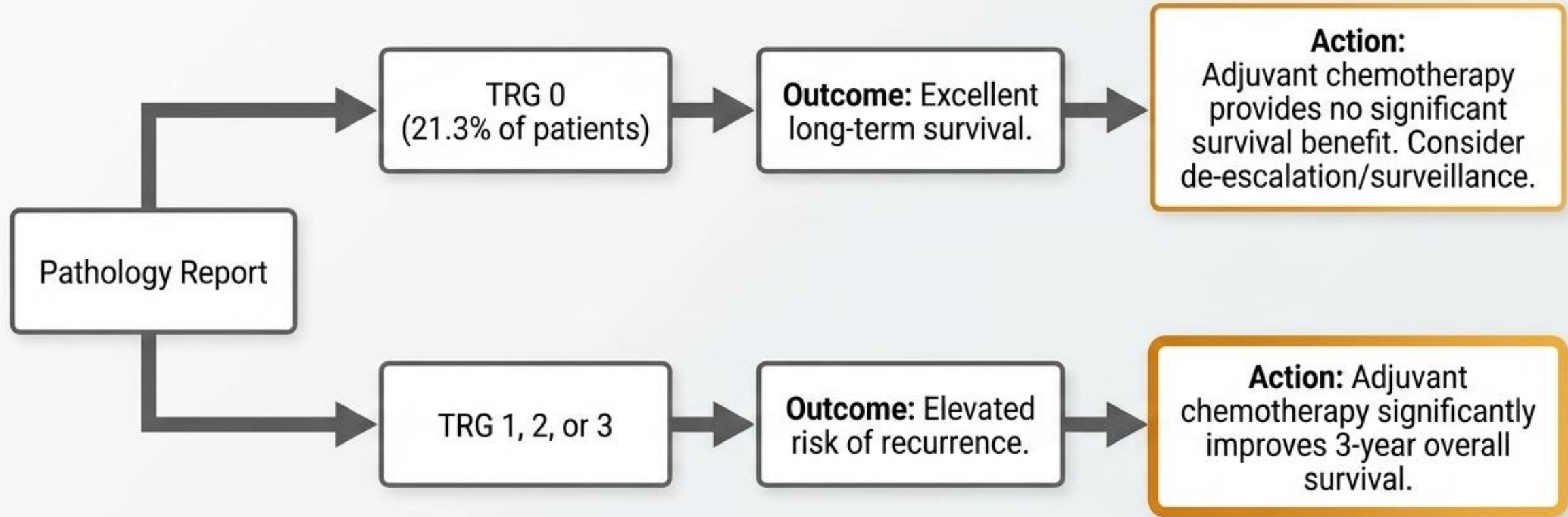
Why Does Treatment Response Matter?

- **Tumor sensitivity:** How effectively did treatment eliminate tumor?
- **Prognosis:** Better regression is generally associated with better outcomes.
- **Multidisciplinary planning:** Response is interpreted alongside: ypT, ypN, CRM, LVI, PNI, Tumor deposits, Molecular findings

A meta-analysis demonstrated significant associations between tumor regression grade and long-term outcomes.



TRG as the Adjuvant Chemotherapy Gatekeeper



Case Scenario

Large fibrotic tumor bed following neoadjuvant treatment.

Does a large tumor bed mean a large amount of residual tumor?

Answer: No.

The pathologist must determine whether the tumor bed contains:

- No viable tumor
- Rare residual tumor cells
- Significant residual carcinoma

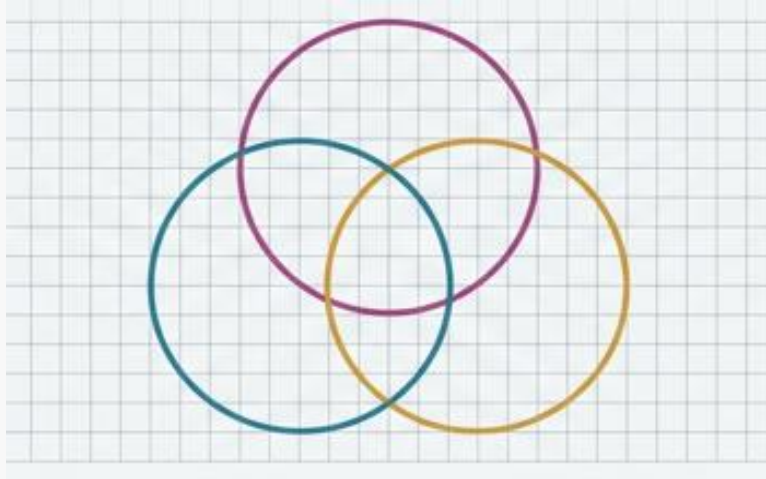
Key concept

Tumor bed size $\neq$ residual viable tumor burden



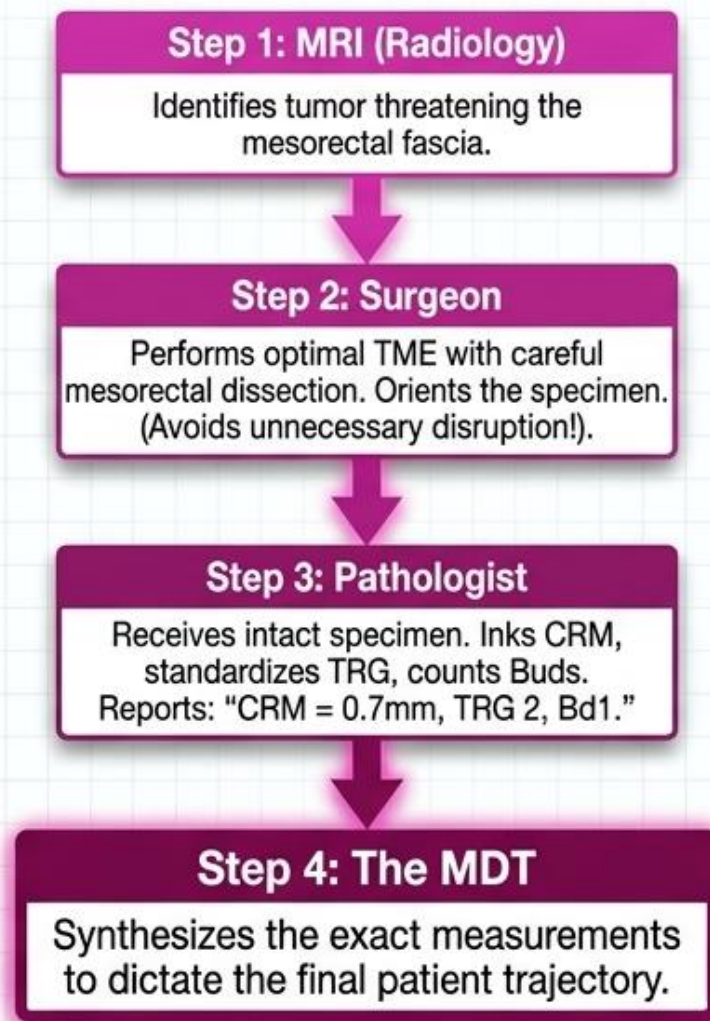
PUTTING THE THREE TOGETHER

Three Pathology Parameters, Three Questions



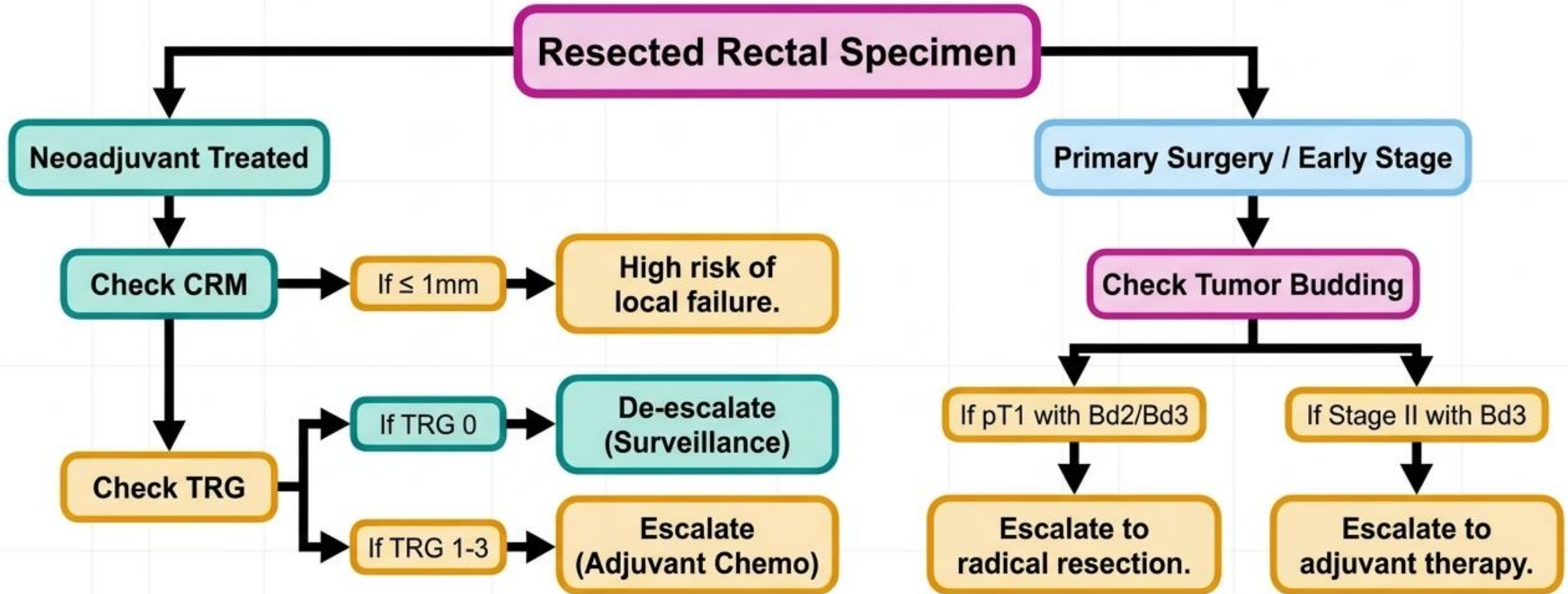
Parameter	The surgeon's question
CRM	Did we achieve adequate radial clearance?
Tumor budding	How aggressive is the tumor biologically?
Treatment response	How much viable tumor survived treatment?

The Multidisciplinary Feedback Loop



Core Message: The pathology report completes the story started by imaging and surgery.
Better specimen = Better staging = Better patient care.

The Post-Operative Decision Nexus



Modern rectal cancer management is no longer guided by TNM staging alone. CRM, TRG, and Budding form a precision triad that dictates the true postoperative trajectory.

Take-Home Messages



- **CRM: Measures surgical clearance and provides important prognostic information.**
- **Tumor budding: Provides additional information about aggressive tumor biology.**
- **Treatment response: Shows how much viable tumor remains after neoadjuvant treatment.**
- **And most importantly: Good pathology starts with good surgery and good communication.**



Pathology is not the last step of surgery; it is part of the decision-making process