CHAPTER 10
Pathological Effects of Neoadjuvant Treatment

The increasing use of RT or CRT in rectal cancer has created new challenges for pathologists, particularly related to the evaluation of morphological changes and tumor response to preoperative treatment. And it has also raised a question about the value that these findings could imply in the prognosis. Neoadjuvant treatment, mainly long-course regimens, but also short-course regimens with long wait, alters the macro and microscopic evaluation and the prognostic relevance of some well-recognized pathological characteristics, such as TNM staging, CRM and lymphatic invasion. The change in the stage that can go from a mild response to the complete disappearance of the tumor (pCR) has already been described as a favorable consequence of these treatments. Thus, we speak of tumor regression (reduction in the amount of neoplastic tissue, regardless of the size of the mass), downsizing (decrease in tumor size, which does not mean a change in T factor), downshifting (decrease in T or N factors, no change in stage), downstaging (decrease in stage) and cCR or pCR. Furthermore, it is interesting that these changes appear to have the same or greater prognostic implication than the initial clinical staging.

TABLE 12: TUMOR REGRESSION GRADE

TRG	Definition
0	No regression
1	< 25 % tumor mass
2	25-50 % tumor mass
3	> 50 % tumor mass
4	Total regression

TABLE 13: DISEASE-FREE SURVIVAL RATES ACCORDING TO TRG AND TNM

yp/TRG	DFS 5 ys	DFS 10 ys
T0	86	90
T1	95	95
T2	81	78
T3	65	66
T4	42	40
N0	85	84
N1	65	59
N2	18	28
TRG 4	86	90
TRG 2-3	75	74
TRG 0-1	63	63

Effects of neoadjuvant treatment on the primary tumor and mesorectal lymph nodes

A common effect is that neoadjuvant therapy often significantly reduces the number of retrieved lymph nodes. This could lead to underestimation of stage N in the absence of a rigorous lymph node search. Furthermore, controversy persists over the optimal distal and circumferential margins.[90]

One study evaluated the distribution of residual cancer cells (RCC) within different layers of the rectal wall in surgical specimens and the value of biopsies of the primary rectal lesion after CRT.[253] One hundred seventy-eigth patients were evaluated, 79 of whom had a biopsy of the primary lesion after CRT, prior to surgery. The distribution of RTC in the surgical specimen, and sensitivity and specificity of the biopsy for the pathological response were analyzed. Of the 120 patients without pCR, the detection rate of RCC in the mucosa, submucosa, and muscularis propria was 20, 36.7, and 69.2%, respectively. The sensitivity and specificity of the biopsies was 12.9 and 94.1%, respectively. This study showed that RCC after CRT are mainly found in the deeper layers, which explains why post-neoadjuvant biopsy is unreliable.

Effects of neoadjuvant treatment on LLNs

A very topical issue in the management of rectal cancer is the involvement of LLNs, that is, the extra-mesorectal pelvic nodes, located in the iliac chains and the obturator region. Their existence has been clearly demonstrated, as well as their prognostic value.[96,156,230,231] There is also enough literature to support that the existence of metastatic involvement at this level does not necessarily imply incurability. And, in the same way, lateral pelvic lymphadenectomy (LPL), widely indicated by Japanese surgeons, has been shown to have a positive effect in patients with locally advanced low tumors.[51,62,97] Since neoadjuvant RT includes the lateral regions in the ra-

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TABLE 14: COMPARATIVE SUMMARY OF THE DIFFERENT TUMOR REGRESSION SCORES

Grade	Ryan	Mandard	AJCC 2010	Rödel	Dworak
0	Complete response		No residual tumor	No regression	No regression
1	Near complete response	Absence of residual tumor	Tumor cells or groups of isolated cells	Regression of < 25% tumor mass	Minimal regression (predominant tumor and fibrosis)
2	Partial response	Small tumor in fibrous tissue	Residual tumor with desmoplastic response	Regression of 25-50% tumor mass	Moderate regression (predominant fibrosis)
3	Poor response	Predominant fibrosis with a greater amount of residual tumor	Minimal evidence of response	Regression of > 50% tumor mass	Near complete regression (fibrosis with minimal residual tumor)
4		Predominant tumor over fibrosis		Complete regression	Complete regression
5		No changes			

diation field, it has been debated whether LPL is necessary or could be replaced by neoadjuvant therapy. With the evidence published to date, some conclusions can be drawn in this regard:

- First, neoadjuvant RT is effective in eradicating LLNs in a significant proportion of patients, but when they are > 7 mm in diameter on HR-MRI, relapses are frequent. In this sense, a study published in 2019 in JCO showed that local relapses in the lateral region are significantly more frequent when LLNs are > 7 mm (19.5% vs. 4.9%, p = 0.045).[164]
- But it was also observed that after neoadjuvant CRT, in patients with LLNs > 7 m the number of local relapses in the lateral region decreased from 19.5% to 5.7% when LLP was added (p = 0.042) .

In light of these results, it is recommended to proceed to LLP regardless of response, when suspicious LLNs > 7 mm in diameter are found at initial staging.

Everything mentioned above explains the extremely important role that pathologists play in the care of rectal cancer patients treated with neoadjuvant therapy and that they are major players in IDT.This implies from the proper handling of the macroscopic specimen, to the precise microscopic evaluation of prognostic factors.

Neoadjuvant response scores

Different scores were described to quantify the level of tumor response to neoadjuvant treatment. These scores evaluate the degree of tumor regression or tumor regression grade (TRG), according to the level of fibrotic component and the percentage of viable tumor cells (Table 12).

The correlation of these scores with long-term survival has also been analyzed and it has been shown that the greater the response, the longer the survival at both 5 and 10 years[58,110] (Table 13).

Table 14 summarizes all the tumor regression scores described.

These scores can also be used to define behaviors after surgery, such as the indication for adjuvant treatment. Although they do not evaluate lymph node disease, the correlation between the degree of response of the tumor to neoadjuvant disease and the response of lymph node disease is a line of research that could have some implication. Through the use of these scores adapted to the images, it could even be possible to define surgical strategies after neoodjuvant treatment, such as the indication of a local resection.