CHAPTER 14
Prognosis After Neoadjuvant Treatment

Although there are conflicting data, they generally suggest that long-term excellent outcomes can be expected in patients with a complete or nearly complete pathologic response.[15,68,79,165,181,189,190,193,214,241]

As an example, a MSKCC retrospective analysis of 200 patients with locally advanced rectal cancer showed a significant improvement in 5-year OS and DFS for those with pCR after preoperative CRT, compared to those with no response (96 vs. 54% and 90 vs. 68%, respectively).[214] Similarly, patients with pCR (N = 60) developed significantly fewer distant relapses (N = 140) (3 vs. 36%).

The performance of clinical trials in colorectal cancer has historically been based on variables such as DFS or OS, which require long-term follow-up. Its replacement by shorter-term criteria could accelerate the progress of scientific investigation, if its reliability in establishing the success or failure of an experimental intervention could be determined. There have been few alternatives in clinical trials for rectal cancer, of which pCR (ypT0N0) is the most widespread. In another chapter were already mentioned the prognostic implication of TGR, and in particular that of pCR.

In 2019, a study was published that analyzed the prognostic implication of budding (cell arrangement in the front of tumor advance), in a population of 124 patients treated with neoadjuvant CRT.[225] A budding rate of 36.[9%] and 55% was observed, with two different techniques, and it was significantly associated with high stages of ypT and ypN, poor differentiation and low degrees of tumor regression. Furthermore, it was strongly predictive of a worse outcome (tumor recurrence or death). In multivariate analyzes, budding was the only significant parameter for OS, even higher than the ypT and ypN stages.

The Neo-Adjuvant Rectal score (NAR score) was recently described for this purpose. It is based on variables routinely collected and readily available to clinical investigators during prospective studies and has been shown to predict OS better than pCR. From the nomograms described by Valentini et al.[233] to predict local recurrence, metastatic disease and OS in rectal cancer, this score was developed to predict OS after neoadjuvant treatment. Unlike pCR, which represents a dichotomous variable, NAR score is a continuous variable that range from 0 to 100, in which higher values imply a worse prognosis. For its calculation, only stage cN and stages cT and pT are used[221] (Fig. 14).

$$NAR = \frac{[5\,pN - 3(cT - pT) + 12]^2}{9.61}$$

Figure 14: NAR score formula.

The NAR score was validated using the NSABP R-04 clinical trial database that enrolled 1479 patients with stage II-III rectal cancer and randomized them to one of four neoadjuvant CRT arms: 1) continuous infusion 5-FU, 2) continuous infusion 5-FU plus oxaliplatin, 3) daily oral capecitabine, or 4) daily oral capecitabine plus oxaliplatin.256 The NAR score was classified as low (<8), intermediate (8-16) and high (>16) based on tertiles of the observed scores and was significantly associated with a 5-year OS of 92, 89, and 68%, respectively (p <0.0001).

However, the NAR score has some inconsistencies. First, since it takes into account the magnitude of downshifting, when pCR occurs in an early T tumor, the score is higher (associated with a worse prognosis) than in initially more advanced tumors. On the other hand, the NAR score also does not include initial lymph node staging (subject to imperfect sensitivity on HR-MRI).

The response rate seems to correlate with the prognosis. The greater the downstaging, the better the survival.