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Mini Review

Is Microsatellite Instability Important in Response to Radiotherapy in Patients with Rectal Cancer?

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ABSTRACT

MSI is the indicator of a DNA repair error that may lead to mutation accumulation formed in the cell. Although there are conflicting studies in the literature, in many studies it has been revealed that MSI has predictive and prognostic effect on response to RT in rectal cancer.

Cancer is a disease that is as a result of the accumulation of many genetic alterations. As a result of these genetic alterations, genomic instability occurs in both nuclear and mitochondrial genome. One of the best indicators of the genomic instability is microsatellite instability. Microsatellites are formations distributed throughout the human genome and that do not encode proteins in their DNA structure in the form of mono, di, tri, tetra, penta dinucleotide repeats, but whose present functions are not known precisely. As the number of the repeats increases in microsatellites, the possibility of error occurrence as insertion or deletion during DNA replication also increases [1-3].

In a normal cell, these errors are recognized by mismatch repair genes (MMR) and directed to the cell repair or apoptosis. Microsatellite instability (MSI) causes function incompetence in the relevant proteins as a result of the mutation or epigenetic alteration in any of the genes (MLH1, MSH2, MSH6, PMS1, PMS2, MLH3, EXO1) encoding proteins that play role in the mismatch repair. It is argued that MSI occurs in the early stages of carcinogenesis and predisposes to consecutive mutations of other responsible genes [1-5]. MSI is detected in 90% of familial colorectal cancers and 75% of endometrium cancers. MSI is also observed in 15% of sporadic colorectal cancers, 2-8% of rectal cancers and 9-45% of sporadic endometrium cancers. It has also been stated that it is seen in solid tumors such as ovary cancer and malignant melanoma [1, 4-7]. It is also thought that frequent detection of MSI outside the specific patient group may lead to new approaches in screening, diagnosis, staging and treatment.

There is a worldwide consensus that the prognostic value of MSI establishes a prediction for treatment. However, the knowledge is limited, and the field is open to the research. In recent years it has been reported that there is also an increase in sporadic cases about colorectal cancer development via MSI. It has been revealed that MSI is both prognostic and predictive in these cases [4, 5, 7]. In a systematic analysis by Popat *et al.*, it is emphasized that MSI tumors in colorectal cancers have better prognosis, tend to metastasize less and respond chemotherapy better when compared to stable tumors. According to the result of this analysis, MSI increases prognostic value in colorectal cancers [4]. MSI presence in endometrium cancer has been shown to be associated with poor prognosis as distinct from colon and gastric cancers [7-9]. It is unclear whether MSI is a sensitivity predictor of radiotherapy (RT). There are few studies in the literature. In a study conducted by Demes *et al.*, the positivity of MSI in rectal cancers was in 8% of the cases, and it was reported that these cases did not respond chemoradiotherapy [6]. In addition, they emphasized in another study

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that MSI did not have role as a predictor for the treatment in local advanced stage rectal cancer patients who received neoadjuvant RT, but it had prognostic significance in lymph node-negative patients [2]. Bilbao-Sieyro *et al.* reported that patients with MSI among diploid tumors in endometrioid endometrial cancer were found to have worse survival rates and lower RT responses [9].

As a consequence, the interest in the significance of genetic alterations in cancer has been increasing day by day and the obtained results seem to be encouraging. MSI is the indicator of a DNA repair error that may lead to mutation accumulation formed in the cell. Although there are conflicting studies in the literature, in many studies it has been revealed that MSI has predictive and prognostic effect on response to RT in rectal cancer. There is a need for large-scale, randomized and prospective multivariate studies to form a consensus on this issue.

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