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Histopathological Analysis of 173 Consecutive Patients with Colorectal Carcinoma: A Pathologist's View

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Background: Worldwide, colorectal carcinomas are the third most common carcinomas in men and the second most common carcinomas in women. Pathological examination of rectum specimens requires special attention for correctly evaluating many prognostically important factors. In this study, we present pathological results of 173 lower anterior resection (LAR) and abdominoperineal resection (APR) specimens retrospectively evaluated.

Material/Methods: We included 173 LAR and APR specimens in this study. Patients were evaluated in the Istanbul Ekin Private Pathology Laboratory and underwent surgery at Çanakkale State Hospital, General Surgery Clinic.

Results: Of the 173 specimens, 15 (8.7%) were APR and 158 (91.3%) were LAR specimens. Ninety-four patients (54.3%) were males and 79 patients (45.7%) were females. The mean age of the patients was 63.5 years (range 26–90 years). In the histopathological examination, malignant neoplasm was detected in 172 of the cases (99.4%) and benign endometriosis was detected in 1 of the cases (0.6%). There were 151 (87.2%), 8 (4.6%), 5 (2.9%), 1 (0.6%), 1 (0.6%), 1 (0.6%), 1 (0.6%), and 4 (2.3%) patients with adenocarcinoma, mucinous adenocarcinoma, intramucosal adenocarcinoma in the setting of a high-grade tubulovillous adenoma, synchronous colon/prostate adenocarcinoma, malignant melanoma, signet ring cell carcinoma, gastrointestinal stromal tumor, endometriosis, and adenocarcinoma diagnosed by the examination of colonoscopic biopsy specimens that showed complete regression with neoadjuvant therapy, respectively.

Conclusions: When evaluating specimens from patients with colorectal carcinoma, pathological evaluation, which is one of the most fundamental pillars in managing patients with cancer, must be performed carefully and meticulously. Each pathological parameter should be evaluated carefully and clinicians and pathologists should evaluate these cases together.

MeSH Keywords: Pathology • Rectal Neoplasms • Rectum

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Background

Worldwide, colorectal carcinomas are the third most common carcinomas in men and the second most common carcinomas in women [1]. A study conducted in 2014 reported that there are approximately 10 000 new cases of colon cancer and nearly 40 000 new cases of rectal carcinoma annually in the United States. Deaths due to colorectal cancers account for approximately 9% of all cancer-related deaths [2]. With changes in oncological treatments over the years, care should be taken to accurately perform pathological and clinical staging of these cases.

Pathological examination of rectum specimens requires special attention for correctly evaluating many prognostically important factors. Careful pathological examination is extremely important with respect to tumor invasion depth, surgical margin status, presence of lymphatic/vascular/perineural invasion, presence/absence of metastatic lymph nodes, presence of neoadjuvant therapy, and regression rates [3].

Pathologists should report the findings clearly. In evaluation of surgical margins, regularity of margins in the mesorectum indicates the success of surgical excision. The number of lymph nodes obtained largely depends on the meticulousness of the pathologist finding them [4].

Because evaluation of the tumor region and the level of peritoneal involvement reflect lymph node metastasis, pathologists play an important role in managing rectal carcinoma cases and in choice of treatment modalities, [5].

In this study, we present pathological results of 173 lower anterior resection (LAR) and abdominoperineal resection (APR) specimens that we evaluated retrospectively over a 6-year period.

Material and Methods

We evaluated a total of 173 rectum LAR and APR specimens at Istanbul Ekin Private Pathology Laboratory between January 2010 and January 2016 from patients operated on at Çanakkale State Hospital, General Surgery Clinic between January 2015 and January 2018.

Patients were excluded if data were missing. Demographic data, etiology, and physiological and surgical parameters were collected from medical records and surgical notes. A data form was created for each patient. Detailed information about the operation was provided to the participating patients and written informed consent was obtained from each one. The study was conducted in accordance with the Declaration of Helsinki.

Table 1. Distribution of LAR and APR cases.

APR	LAR	Total cases
n=15 (%8.7)	n=158 (%91.3)	n=173

LAR – low anterior resection; APR – abdominoperineal resection.

For all specimens included in this study, we assessed tumor invasion depth, surgical margin status, lymphovascular/perineural invasion, presence/absence of metastatic lymph nodes, neoadjuvant therapy, and regression rates.

When performing lymph node dissection, adipose tissue specimens were kept in alcohol overnight and were dissolved and solidified into adipose tissue components.

For all specimens, we accurately evaluated all surgical margins when macroscopically sampling TME specimens, as well as performing initial staining with ink and sampling by slicing from the distal to proximal side. Some suspicious slices were sampled with megablocks.

Results

Of the 173 specimens evaluated, 15 were APR (8.7%) and 158 were LAR (91.3%). Of the 158 LAR specimens, 7 (4.1%) were obtained by intersphincteric very low anterior surgeries (Table 1).

Ninety-four patients (54.3%) were males and 79 patients (45.7%) were females. The mean age was 63.49±11.96 years (range 26–90 years).

In the histopathological examination, malignant neoplasms were detected in 172 of the cases (99.4%) and benign endometriosis was detected in 1 of the cases (0.6%).

Twenty-four patients (13.9%) (APR=2, LAR=22) had undergone neoadjuvant therapy. Of these 24 patients, 5 (2.9%) showed mild, 7 (4.1%) showed moderate, and 8 (4.6%) showed high treatment response, whereas 4 patients (2.3%) had complete regression and no residual tumor was found (Table 2, Figure 1).

All surgical margins were negative in 169 specimens (97.7%), whereas a tumor was present in the distal surgical margins in 3 specimens (1.7%) (Figure 2). One case (0.6%) was benign (endometriosis).

Lymph node metastasis was observed in 78 patients (45.1%), whereas no metastasis was observed in 95 patients (54.9%). The minimum and maximum number of lymph nodes dissected from the specimens were 0 and 43, respectively, with a mean of 14.8. In specimens from patients who had undergone neoadjuvant

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Table 2. Regression responses of neoadjuvant treated patients.

Mild treatment response	n=5 (%2.9)
Moderate treatment response	n=7 (%4.1)
High treatment response	n=8 (%4.6)
Complete regression	n=4 (%2.3)
Total	**n=24 (13.9%)**

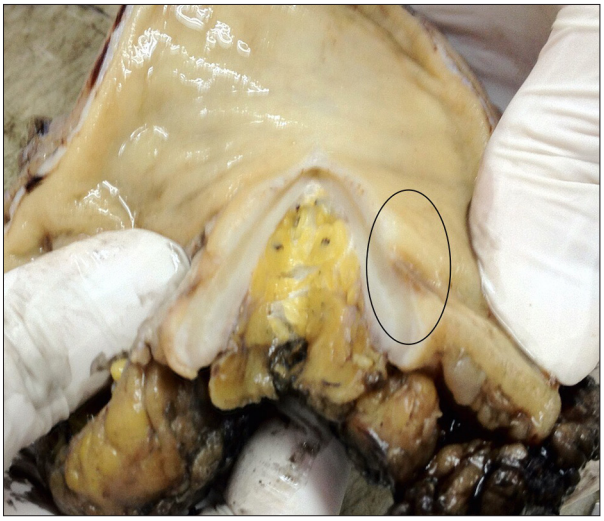

Figure 1. Rectal mucosal flattening and mucosal ulcer in the focal area in the LAR specimen with complete regression after neoadjuvant therapy.

therapy, the minimum and maximum number of dissected lymph nodes were 0 and 29, respectively, with a mean of 13.1. All of the specimens from which lymph nodes could not be detected were from patients who had undergone neoadjuvant therapy.

Perineural invasion was observed in 58 patients (33.5%) and lymphovascular invasion was observed in 91 patients (52.6%).

Six (3.5%), 34 (19.6%), 98 (56.7%), and 30 (17.3%) patients had stage T1, T2, T3, and T4 disease, respectively. No residual tumor was observed in 4 (2.3%) patients after neoadjuvant therapy, and these patients were evaluated as stage yT0 (Table 3).

With respect to the distribution of cases, 151 (87.2%), 8 (4.6%), 5 (2.9%), 1 (0.6%), 1 (0.6%), 1 (0.6%), 1(0.6%), 1(0.6%), and 4 (2.3%) patients had adenocarcinoma, mucinous adenocarcinoma, intramucosal adenocarcinoma in the setting of a high-grade tubulovillous adenoma, synchronous colon/prostate adenocarcinoma, malignant melanoma, signet ring cell carcinoma, gastrointestinal stromal tumor, endometriosis, and adenocarcinoma diagnosed by the examination of colonoscopic biopsy specimens that showed complete regression with neoadjuvant therapy, respectively (Table 4).

Figure 2. LAR specimen from a patient with intramucosal adenocarcinoma developed in the setting of tubulovillous adenoma, closer than 0.1 cm to the distal surgical margin.

Table 3. Stage distributions of cases.

Stage	Cases
T1	n=6 (3.5%)
T2	n=34 (19.6%)
T3	n=98 (56.7%)
T4	n=30 (17.3%)
yT0	n=4 (%2.3)

Table 4. Distribution of cases.

Tumor type	Cases
Adenocarcinoma	n=151 (87.2%)
Mucinous adenocarcinoma	n=8 (4.6%)
Intramucosal adenocarcinoma developed in the setting of tubulovillous adenoma	n=5 (2.9%)
Synchronous colon/prostate adenocarcinoma	n=1 (0.6%)
Malign melanoma	n=1 (0.6%)
Signet ring cell carcinoma	n=1 (0.6%)
Gastrointesitnal stromal tumor	n=1 (0.6%)
Endometriosis	n=1 (0.6%)
Adenocarcinoma showed complete regression with neoadjuvant therapy	n=4 (2.3%)
Total	**n=173 (100%)**

Discussion

Patients with rectal carcinoma should be managed by a multidisciplinary team of surgeons, pathologists, radiologists, oncologists, radiotherapists, and gastroenterologists [6]. This

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teamwork will have important contributions to the treatment of patients with rectal carcinoma. Physicians should have sufficient knowledge regarding imaging, pathology, treatment modalities, and prognostic factors [7]. In this study, we emphasized the importance of pathologic parameters, particularly in patients with rectal carcinoma, and investigated macroscopic and microscopic parameters individually in patients who underwent total mesorectal excision (TME).

In terms of histologic tumor subtypes, it is known that approximately 90% of cases of colorectal carcinoma are adenocarcinomas. The World Health Organization (WHO) reported numerous subtypes for the remaining cases [8]. Among the other subtypes, mucinous adenocarcinoma is observed in approximately 4–19% of cases, and when a tumor is microscopically evaluated, pools of extracellular mucin should be observed in over 50% cases. If the mucin content is <50%, this must be interpreted as an adenocarcinoma with accompanying mucinous component [9,10]. There are many reported cases of synchronous tumor in the literature, such as small-cell lung carcinoma after lung carcinoid tumor, pancreatic clear cell carcinoma/gastrointestinal stromal tumor of the stomach, gastric/rectal adenocarcinoma, and papillary/medullary thyroid carcinoma. A case series article reported that cases of synchronous prostate and rectum adenocarcinoma were present at very low rates in 3 cases [11,12]. In another case report, it was reported that cases of melanoma with poor prognosis constituted 0.5–2% of all anorectal malignancies and were most commonly seen in the skin and retina, followed by the anorectal region [13]. Gastrointestinal stromal tumors (GISTs) are rare neoplasms arising from mesenchymal precursor cells of the gastrointestinal tract; approximately 5–15% are found in the colon and rectum [14]. Although there are many histological subtypes, our patients were found to have adenocarcinoma.

During pathological evaluation of the lymph node in cases of rectal carcinoma, sufficient surgical resection and meticulous dissection of lymph nodes in rectal specimens by pathologists are of great importance for staging [1]. The minimum number of lymph nodes that should be dissected must be considered. In most guidelines and in the literature, the minimum number of lymph nodes to be obtained is 12. However, it is reported that regression may develop in regional lymph nodes because of advanced neoadjuvant combined chemoradiotherapy, and thus lymph nodes may not be detected. If neoadjuvant therapy has not been administered, lymph node dissection will become more difficult; therefore, dissection should be meticulously performed. If needed, methods that remove the mesorectal adipose tissue, such as methylene blue-assisted lymph node dissection or acetone compression, can be performed [15–18]. Once we have performed necessary macroscopic sampling from the tumor, we kept the adipose tissue in alcohol overnight, and performed sampling from most

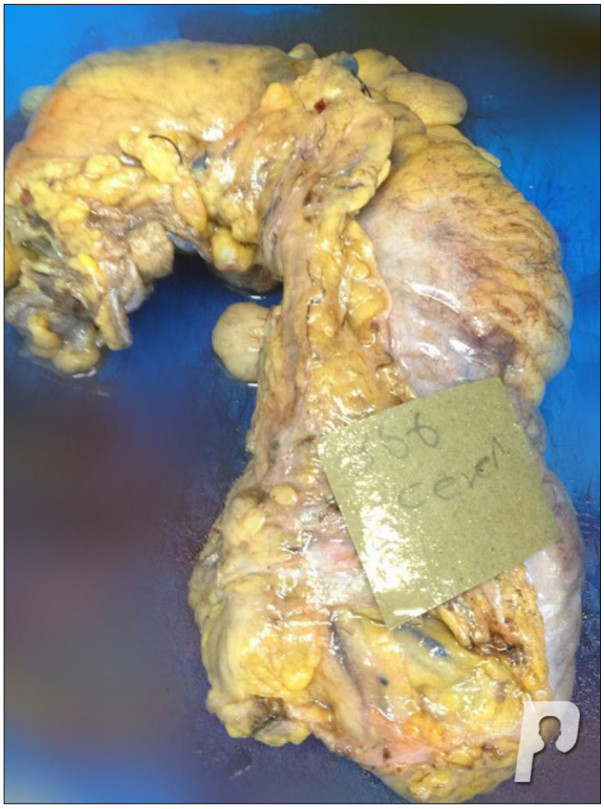

Figure 3. LAR specimen with complete mesorectal integrity.

of, or sometimes from the entire remaining, adipose tissue in specimens where no lymph nodes were found.

In our study, the mean number of dissected lymph nodes was 14.8 when all specimens from patients were included. Conversely, the mean number of dissected lymph nodes was 13.1 from specimens from only patients who had undergone neoadjuvant therapy, which was higher than the minimum required number of dissections. In a study on 186 patients conducted in 2017, when all patients who had and not undergone neoadjuvant therapy were included, the mean number of lymph nodes per specimen was reported as 14 [19]. Another consideration that requires attention while performing lymph node dissection is the distance of the metastatic lymph node to the circumferential surgical margins. During macroscopic and microscopic evaluation, it is absolutely necessary to specify at which surgical margin the metastatic lymph node was present, its distance to this margin, metastatic tumor size, and whether there is perinodal invasion.

With respect to surgical margins, TME is considered as the standard of care in cases of rectal carcinoma. Cases of rectal carcinoma should be considered in terms of local or distant recurrences based on many parameters, such as advanced stage tumor, large tumor size, distal tumor localization, ulcerative/stenotic growth pattern of the tumor, experience

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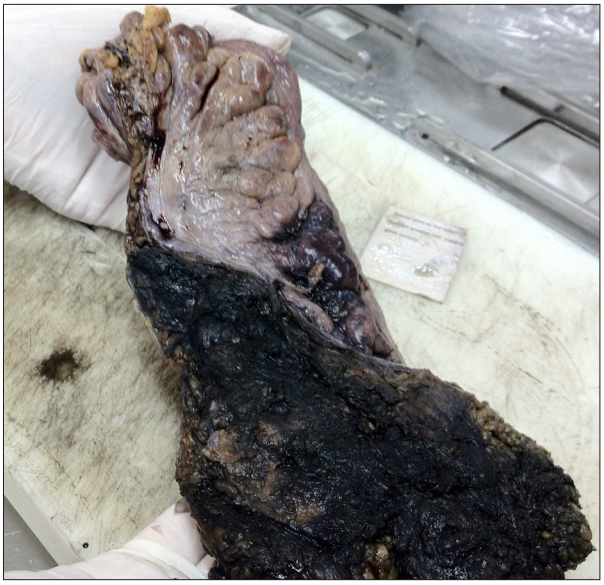

Figure 4. Posterior view of ink-stained LAR specimen for mesorectal radial surgical margin evaluation.

of the surgeon, positive surgical margins on histopathological examination, and presence of vascular invasion. In terms of circumferential surgical margins, appropriate and full surgical removal of the mesorectum is important with respect to subsequent local or distant recurrences that may develop. Macroscopically accurate pathological evaluation of mesorectal integrity and its indication in the pathology report may have an effect on the prognosis of these patients [20]. If possible, TME specimens should be delivered to the pathologist without being fixed, and specimens must not be opened by the surgeon. The mesorectal surface of TME specimens are evaluated under 3 categories: complete, nearly complete, and incomplete. The surface of a mesorectal resection that is evaluated as high quality, good, and complete should be straight and smooth (Figure 3). The distal margin should not be conical and there should not be defects deeper than 5 mm on the mesorectal surface. In case of perforation due to surgical manipulation of the resected specimens or if the muscular layer is observed on macroscopic examination, the specimen should be evaluated as an incomplete resection [6]. For accurately evaluating all surgical margins when performing macroscopic sampling of TME specimens, initial staining with ink and sampling by slicing from the distal to proximal side is recommended and accepted so that all circumferential areas of the mesorectum are visible [6] (Figures 4, 5). We sampled our specimens in this manner, and some suspicious slices were even sampled with megablocks that were approximately 4–5 times larger than normal blocks and examined on megaslides under a microscope. Therefore, we are able to determine the distance of a tumor to surgical margins at a microscopic level (Figure 6). In a study conducted in 2017, both circumferential and distal surgical margins were reported to be negative at a rate of 88.1% [19]. We attribute the high negative rates of surgical margins in our specimens to the experience of our surgeons, the careful macroscopic evaluation of our specimens, and the fact that most of our specimens were complete or nearly complete resections.

In terms of lymphatic, vascular, and perineural invasion, in a study conducted in 2013, the presence of lymphatic invasion was the strongest indicator of early lymph node metastasis

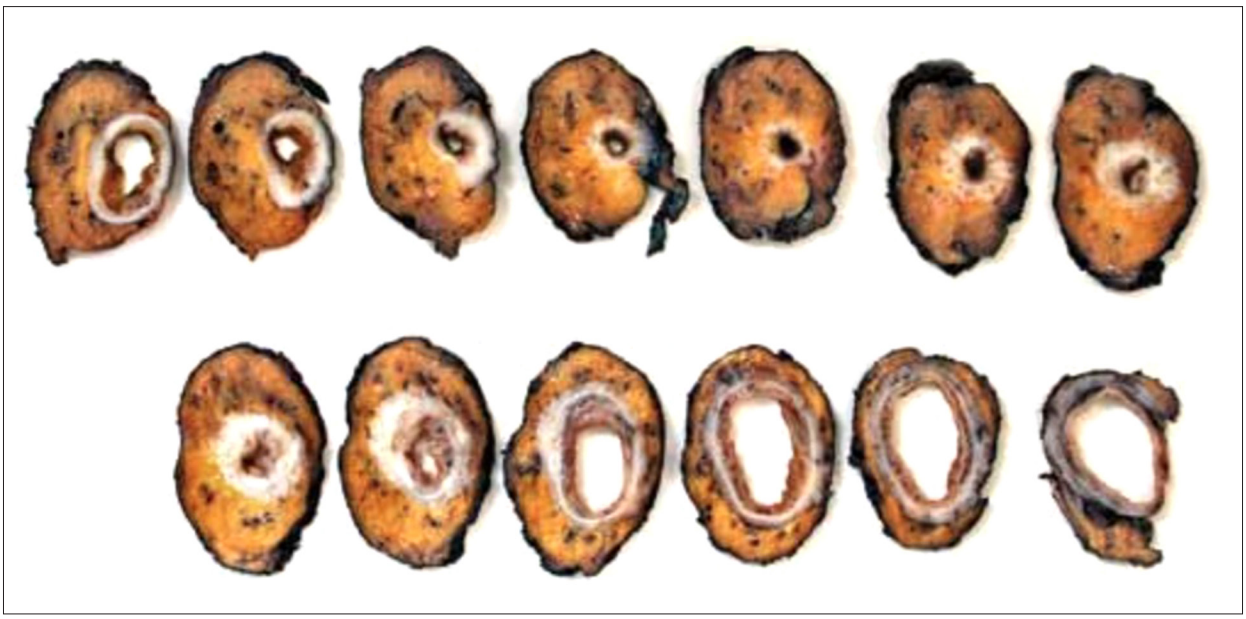

Figure 5. Slice sampling style that covers all circumferential areas, adapted from the method used by Hoorens et al. This figure is taken from the Hoorens et al. study [6].

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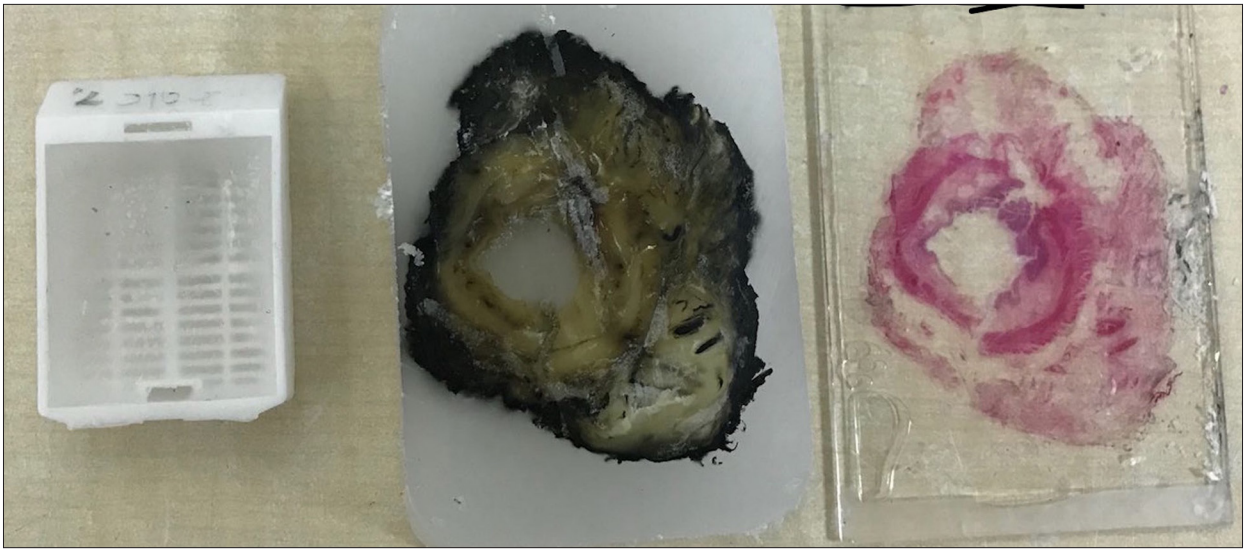

Figure 6. Megaslide and megablock samples (normal-size block on the left) of slice sampled from the LAR specimen tissue for convenient evaluation of the radial surgical margin.

[20,21]. One study reported that lymphovascular invasion was detected in 18% of cases of malignant polyps, and 35% of these cases had lymph node metastasis [22]. In our study, lymphovascular invasion and lymph node metastasis were not observed in any of the 4 patients with intramucosal adenocarcinoma developing in the setting of a high-grade tubulovillous adenoma. The prognostic effect of venous invasion is less pronounced, and its independent prognostic significance could not be determined in many studies [22,23]. Some studies have concluded that the term "lymphovascular invasion" refers to both vascular and lymphatic invasion, whereas other studies suggest that these should be reported separately [24]. The Association of Directors of Anatomic and Surgical Pathology and the College of American Pathologists report that lymphatic and blood vessel invasion should be separately indicated in a pathology report and that these are important prognostic markers [1]. As in some other studies, we separately evaluated lymphatic and vascular invasion parameters in our routine pathology practice and, if necessary, we used a D2-40 (podoplanin) marker for lymphatic and CD31 marker for vascular structures during immunohistochemical analysis [25]. Perineural invasion can be defined as invasion of nerve structures by tumor cells. This condition is usually associated with an aggressive tumor phenotype [26]. In a study conducted on 110 patients in 2017, perineural invasion was reported in 14 (16%) of the patients [27].

In terms of tumor invasion depth and neoadjuvant therapy, it is necessary to take into account the anatomic layers of the colonic wall (i.e., mucosa, submucosa, muscularis propria, mesorectal adipose tissue, and serosa) and to perform staging accordingly when evaluating tumor invasion [28]. In early lesions, which may be polypoid or nonpolypoid lesions, staging grades are different and staging is based on Haggit and Kudo classification [29,30]. In a study conducted on 42 257 patients in 2017, chemoradiotherapy was administered to patients with stage II/III disease before resection, and complete regression was detected in 9.9% patients [31]. There are many sources for grading regression [32]. We generally evaluated our patients according to the grading system of Dworak and Rödel using 4 grades [33–37].

Careful macroscopic/microscopic examination of rectal carcinoma specimens by a pathologist is needed for accurate appraisal of staging and other factors. The role of the pathologist ranges from the histopathological diagnosis to the gross and microscopic examination of the specimens. On this basis, the examining pathologist issues statements that evaluate the quality of the surgical procedure and provide information for therapeutic purposes [3,38].

Conclusions

Pathological evaluation, which is one of the most fundamental pillars of managing patients with cancer, must be performed carefully and meticulously when evaluating patients with colorectal carcinoma. Each pathologic parameter should be evaluated carefully, and clinicians and pathologists should evaluate these cases in cooperation.

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