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Multidisciplinary Treatment Strategy for Early Colon Cancer: A Review-An English Version

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Abstract
Treatment for early colon cancer has progressed rapidly, with endoscopic resection and minimally invasive surgery. It is important to select patients without risk of lymph node metastasis before deciding on endoscopic resection for early colon cancer treatment. Pathological risk factors include histologic grade of cancer cell differentiation, lymphovascular invasion, perineural invasion, tumor budding, and deep submucosal invasion. These risk factors for predicting lymph node metastasis are crucial for determining the treatment strategy of endoscopic excision and radical resection for early colon cancer. A multidisciplinary approach is emphasized to establish a treatment strategy for early colon cancer to minimize the risk of complications and obtain excellent oncologic outcomes by selecting an appropriate treatment optimized for the patient's stage and condition. Therefore, we aimed to review the optimal multidisciplinary treatment strategies, including endoscopy and surgery, for early colon cancer.

Keywords
colonic neoplasms, lymph nodes, endoscopic mucosal resection, minimally invasive surgical procedures, laparoscopy

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Introduction

Colon cancer is one of the most common gastrointestinal cancers in South Korea. As the national cancer screening program has been widely implemented, the detection rate of early colon cancer has increased over the past decades[1]. Treatment for early colon cancer has progressed rapidly, with endoscopic resection and minimally invasive surgery[2].

Endoscopic resection can be performed without general anesthesia and has the advantages of faster recovery, shorter hospital stay, and lower cost than surgical resection[3]. However, endoscopic resection excises only the primary local lesion and cannot perform lymph node resection. Therefore, it is important to select patients without risk of lymph node metastasis before deciding on endoscopic resection for early colon cancer treatment[4].

Minimally invasive surgery has brought about a significant change in the field of colon cancer surgery[5-7]. Laparoscopic surgery has improved short-term postoperative

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outcomes, such as operative pain, recovery of bowel movement, length of hospital stay, and quick return to daily life[8]. Large-scale randomized clinical trials have established the safety of long-term oncological outcomes[9-11]. Therefore, laparoscopic surgery has been accepted as a safe oncologic surgery for patients with colon cancer.

Therefore, a multidisciplinary approach is emphasized to establish a treatment strategy for early colon cancer to minimize the risk of complications and obtain excellent oncologic results by selecting an appropriate treatment optimized for the patient's stage and condition[12]. Therefore, we aimed to review the optimal multidisciplinary treatment strategies, including endoscopy and surgery, for early colon cancer.

Pathologic Risk Factors for Lymph Node Metastasis

The most important determinant of prognosis in early colon cancer is lymph node metastasis. Preoperative computed tomography (CT) is routinely used to detect lymph node metastases. Morphological features of lymph nodes, such as border irregularities, nodal texture heterogeneity, and shape, are considered distinguishing features of metastatic nodes. Lymph nodes with homogenous density are less likely to be metastatic, whereas lymph nodes with irregular borders or mixed densities are considered metastatic nodes[13]. Although lymph node metastasis is evaluated using various radiologic features, the diagnostic accuracy of lymph node metastasis based on CT scans is still only approximately 70%. Approximately 15%-20% of lymph nodes smaller than 5 mm are reported to be metastatic lymph nodes in colon cancer[14,15].

Therefore, pathological risk factors for predicting lymph node metastasis are very important when determining the treatment strategy of endoscopic excision and radical resection for early colon cancer[16]. Pathological risk factors include the histologic grade of cancer cell differentiation, lymphovascular invasion, perineural invasion, tumor budding, deep submucosal invasion, and vertical invasion depth (>1,000 μm)[17]. Therefore, inclusion of submucosal tissue is important for pathological evaluation.

Poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma could be classified as poor histologic types[18]. Lymphatic and venous invasion are also independent predictors of lymph node metastasis[19]. Tumor budding is defined as the presence of a single cancer cell or cluster of fewer than five cancer cells isolated from the tumor at the invasive front of submucosal infiltration[20]. The presence of 5-10 tumor buddings at the site of the deepest invasion front could increase the risk of lymph node metastasis in early colon cancer[21].

Colon cancer confined to the mucosal layer does not cause lymph node metastasis. However, if it invades the submucosal layer, lymph node metastasis occurs in approximately 6%-20% of cases[22]. The Haggitt classification method was used to evaluate submucosal invasion of pedunculated lesions. For nonpedunculated lesions, the depth of submucosal invasion was evaluated according to the Kudo or Kikuchi classification[23]. When the submucosa is divided into levels, it is divided into the superficial submucosal (SM1), middle (SM2), and deep layers (SM3). Deep submucosal invasion with Haggitt level 4 and Kikuchi SM 2-3 increases the risk of lymph node metastasis[24]. In nonpedunculated malignant polyps, the risk of lymph node metastasis increases more than 3-fold when the depth of vertical invasion is greater than 1,000 μm of the submucosal layer[25]. If the entire thickness of the submucosal layer cannot be excised by endoscopic resection, it could be inaccurate to divide the submucosal layer into three levels. Therefore, a vertical invasion depth of more than 1,000 μm could be used as an alternative feature to reflect deep submucosal invasion. The resection margin involved after endoscopic removal is also a risk factor[26,27]. Additional radical resection is required in the presence of these risk factors (Figure 1)[28].

Endoscopic Optical Assessments

Prediction of the depth of invasion in early colon cancer through endoscopic optical assessments is important to determine the appropriate treatment method for endoscopic or surgical resection. The hardness of the lesion, deep and irregular depression, unchangeable shape by air injection, convergence of mucosal folds, and nonlifting signs are macroscopic findings that suggest deep submucosal cancer[29]. The nonlifting sign is known to suggest submucosal fibrosis or deep submucosal invasion. However, it has lower sensitivity and accuracy than the prediction of deep submucosal carcinoma by gross morphology, thereby limiting the usefulness of predicting deep submucosal invasion[30].

Optical assessment of pit patterns and vascular patterns is useful for estimating the depth of submucosal invasion using magnifying chromoendoscopy and narrow-band imaging endoscopy. Deep submucosal invasion can also be predicted using Kudo's pit pattern. In pit pattern types III_L, III_S, and IV, the incidence of deep submucosal invasion was only 1%, 5%, and 8%, respectively. If the shape is irregular (type V_I) or nonorganized (type V_N), the probability of deep submucosal invasion is 14% and 80%, respectively[31]. After applying the dye solution, the mucosa was observed using magnifying chromoendoscopy to evaluate the shape of the mucosal gland orifice. Indigo carmine and crystal violet are mainly used for magnifying chromoendoscopy, and we found no difference in diagnostic accuracy between the two staining methods[32]. The narrow-band image (NBI) selec-

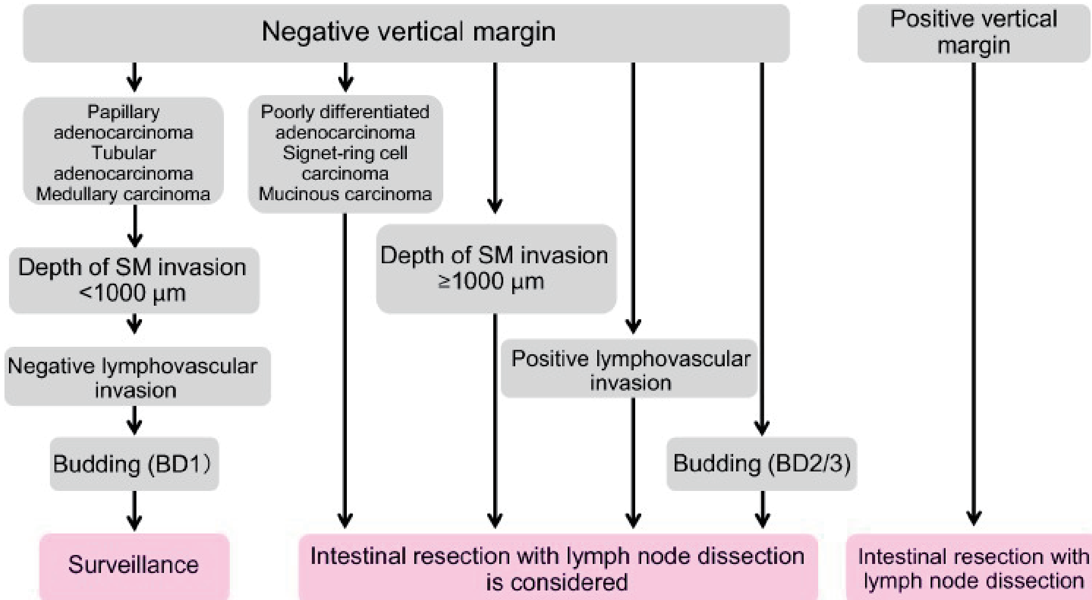

Figure 1. Treatment strategies for pT1 cancer after endoscopic resection. Adapted from Hashiguchi et al. [28], according to the Creative Commons License of open access. SM, submucosa; BD, budding degree

tively controls the wavelength of light and allows detailed examination of the mucosal surface using shallow light transmittance. NBI using magnifying endoscopy enables the exploration of the capillary pattern of the mucosal surface. NBI can predict the risk of invasive colon cancer by evaluating mucosal color, surface morphology, and capillary pattern[33]. If the pit pattern is broken, the thick microvasculature moves irregularly, or an avascular area is observed. While the vascular distribution is not uniform, the deep submucosal layer has likely invaded[34].

Classification of capillary patterns using magnifying endoscopy can be performed more precisely. Various evaluation tools have been developed in Japan, such as the Sano, Hiroshima, Showa, and Jikei classifications. The Japan Narrow Band Imaging Expert Team (JNET) classification was proposed as an integrated classification system in a consensus meeting, and its usefulness has been demonstrated through validation studies. An endoscopy expert group formed by Japan, the United States, and Europe developed the Narrow Band Imaging International Colorectal Endoscopic (NICE) classification for the endoscopic diagnosis of early colon cancer[35]. The NICE classification is able to differentiate benign adenoma, intramucosal carcinoma, superficial submucosal carcinoma, and deep submucosal carcinoma based on microscopic changes in the mucosa that can be observed endoscopically (Table 1). The possibility of deep submucosal invasion is high if the findings are suggestive of deep submucosal cancer on macroscopic endoscopy, if the Kudo progenitor form is V_N, or if it falls under Sano class IIIB, Hiroshima class C3, or JNET class 3 on narrow-band imaging endoscopy. Therefore, surgery can be considered based on endoscopic optical diagnosis.

The Dutch T1 colorectal cancer working group performed a multicenter prospective evaluation of real-time optical diagnosis of T1 colorectal cancer in large nonpedunculated colorectal polyps using narrow-band imaging. The sensitivity of optimal diagnosis is still limited at 63.3%, but the specificity of predicting endoscopically unresectable lesions with deep submucosal invasion is accurate at 99.0%[36]. Thus, the use of advanced endoscopic imaging techniques, including magnifying chromoendoscopy and narrow-band imaging, could increase the accuracy of differentiation between the shallow or deep submucosal invasion of early colon cancer and reduce unnecessary surgical referral for lesions amenable to endoscopic resection[32]. Conversely, it can reduce unnecessary preoperative endoscopic resection for lesions that require immediate surgical resection and help patients economically.

Endoscopic Treatment

Colon cancer confined to the mucosal layer has no risk of lymph node metastasis. Therefore, if the intramucosal tumor is completely resected by endoscopic resection, recurrence is not possible, and treatment can be terminated. The recurrence rate between endoscopic and surgical treatments did not differ in case of mucosal and shallow submucosal invasion filtration[37].

However, endoscopic resection of submucosal colon cancer with a high risk of lymph node metastasis has a higher recurrence rate than surgical resection. Endoscopic resection had a local recurrence rate of 2.3%-6.4%, whereas surgical

Table 1. Narrow Band Imaging International Colorectal Endoscopic (NICE) Classification for the Endoscopic Diagnosis of Early Colorectal Cancer.

	Type I	Type II	Type III
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels may be present coursing across the lesion	Brown vessels surrounding white structures	Has area of disrupted or missing vessels
Surface pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular, or branched white structures surrounded by brown vessels	Amorphous or absent surface pattern
Most likely pathology	Hyperplastic and sessile serrated polyp	Adenoma	Deep submucosal invasive cancer

Adapted from Wang et al. [35], according to the Creative Commons License.

resection showed a relatively low local recurrence rate of 0.9%-1.9% in early colon cancer with submucosal invasion[38]. For early colon cancer with or without risk factors, the lymph node metastasis rates were 15.5% and 7.1%, respectively[39]. Therefore, additional surgery is required following endoscopic treatment for early colon cancer with high-risk factors for lymph node metastasis.

Endoscopic treatments include cold snare polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). When a malignant colon polyp is observed on colonoscopy, the polyp size and gross morphology based on the Paris classification must be identified[40]. Pedunculated malignant polyps can be removed safely using cold snare polypectomies. For nonpedunculated polyps, an appropriate method for endoscopic resection can be selected based on tumor size. Polyps smaller than 2 cm in size can be resected safely through EMR, and those larger than 2 cm can be resected safely through ESD[41]. Non-pedunculated polyps with depression (type IIc) may be associated with submucosal invasion[42].

Resection margin involvement of cancer cells is the most important factor leading to oncological failure of local excision[43]. Therefore, en bloc resection with a negative resection margin should be performed for endoscopic treatment of early colon cancer. ESD could be more favorable for en bloc resection of large nonpedunculated lesions than the EMR technique[44]. However, ESD carries a high risk of complications, such as bleeding and perforation[45]. ESD for colon lesions has a high degree of difficulty; thus, complication rates and complete resection rates vary significantly depending on the experience and technical skill of the endoscopists[46]. Further, most of the complications after submucosal dissection can be treated with an endoscope, and emergent surgical intervention is required in only approximately 1% of submucosal dissection cases; thus, the safety of ESD is acceptable[47]. Therefore, ESD of the colon should be performed at a medical institution where an endoscopy specialist with sufficient experience after proper training can cope with emergencies caused by complications related to the procedure[48].

However, not all patients with early colon cancer are indicated for endoscopic resection.

In early colon cancer, endoscopic resection has the advantages of fewer adverse reactions, shorter hospital stay, lower cost, and long-term preservation than surgical resection. The superficial submucosal layer lacks lymphatic channels; therefore, there is little risk of lymph node metastasis. Thus, endoscopic resection can be safely performed for superficial submucosal invasion. Deep submucosal invasion raises the possibility of lymphovascular invasion and lymph node metastasis[49]. If deep submucosal invasion is suspected, only a targeted biopsy should be performed, and surgical resection should be considered[50].

Therefore, evaluating the risk factors for lymph node metastasis while selecting endoscopic or surgical resection is important. In addition, an appropriate surgical treatment should be recommended after endoscopic resection to obtain excellent long-term outcomes in patients with early colon cancer with a high risk of lymph node metastasis.

Surgical Treatmet

If the resected tissue has risk factors of lymph node metastasis or involved resection margin, surgical resection should be considered for safe oncologic treatment. The principles of surgical resection for colorectal cancer treatment consist of three components: an intact mesocolic plane, radical lymph node dissection, and a longitudinal resection margin.

Mesocolic plane surgery

In 1982, Bill Heald presented total mesorectal excision (TME) as a sharp dissection along the embryologic plane to remove micrometastatic foci that had spread in the mesorectum. With mesorectal plane surgery, the local recurrence rate of rectal cancer was reduced from 40% to less than 10%.

By improving the surgical quality of TME, oncologic benefits can be obtained for rectal cancer[51]. In 2009, Hohenberger et al. proposed the novel concept of complete mesocolic excision (CME) for colon cancer[52]. CME as mesocolic plane surgery has a concept similar to that of TME as maintaining the intact mesocolic plane using sharp dissection along Toldt's fascia. In a pathological study comparing the quality of mesocolic plane surgery, significant survival differences were reported in the intact mesocolon compared to the incomplete mesocolon with exposing of the muscularis propria[53]. CME showed oncological benefits in the meta-analysis[54].

The conceptualization of CME could provide standardized surgical quality and enable objective analysis through the quantification of surgical treatment. Pathologic evaluation of the dissected mesocolic plane could enable the objective analysis of pathologic quality, which could be translated as an indicator of oncological prognosis and surgical quality[55]. Therefore, awareness of CME in the surgical community could improve surgical quality through the standardization of oncologic surgery for colon cancer.

Radical lymph node dissection

Surgeons must determine the dissection range of the lymph nodes. The diagnostic accuracy of preoperative CT in predicting lymph node metastasis is limited. Although the large size, round shape, and heterogeneous texture of the lymph nodes increase the likelihood of metastasis, CT scans are not reliable for lymph node (N) status. As the depth of tumor invasion increases, the risk of lymph node metastasis also increases[56]. Therefore, preoperative T status plays an important role in determining the extent of lymph node dissection. The Japanese Society of Cancer of the Colon and Rectum (JSCCR) guidelines recommend D3 dissection in advanced colon cancer because the probability of D3 lymph node metastasis in T3-4 is as high as 10%[57]. Central vascular ligation was performed for the completion of mesocolon resection extending to the mesenteric vascular root. For radical lymph node dissection, vascular ligation should be performed at the origin of feeding arteries. This central vascular ligation is similar to the concept of D3 dissection according to the JSCCR guidelines.

The lymphatic pathway of the colon was described by Jamieson and Dobson in the early 20th century. They injected Prussian blue into the colon walls of cadavers, observed the dye flowing along the lymphatic system, and stained the lymph nodes. These studies showed that colon cancer cells could spread out of the colon wall to the regional lymph nodes, highlighting the need for radical lymph node dissection[58].

Radical D3 dissection is based on Gillot's concept of the surgical trunk of the superior mesenteric vein (SMV) for right colectomy. In 1964, Gillot named the area on the right side of the SMV between the gastrocolic trunk and ileocolic vein as the surgical trunk and an anatomical landmark[59]. Since lymphatics from the right colon are collected in the surgical trunk and drained into the central lymphatic system, radical lymph node dissection for locoregional control that includes the surgical trunk area was accepted. In 1995, Toyota et al.[60] explained that lymphatic flow in the right-sided colon forms a lymphatic chain on the right lateral side of the SMV that runs along with the periportal lymphatic system, with some lymphatic connections extending to the lymph node at the root of the middle colic artery.

However, there is a lack of clinical evidence regarding the oncological necessity and benefits of radical lymph node dissection in early colon cancer. Currently, several randomized clinical trials are ongoing to determine the oncologically appropriate lymph node dissection area and the anatomical extent of D3 dissection[61,62].

The prognosis was better in patients with 20 or more resected lymph nodes than in patients with fewer than five harvested lymph nodes[63]. The pathological diagnosis of metastatic lymph nodes may not have been possible because of insufficient lymph node dissection; thus, the treatment opportunity for adjuvant chemotherapy may have been missed. Appropriate chemotherapy with sufficient lymph node dissection may lead to improved survival rates, resulting from more accurate nodal staging. From an oncological point of view, at least 12 lymph nodes should be retrieved to evaluate the pathological stage of cancer, so that patients can receive appropriate chemotherapy after surgery[64].

Longitudinal resection margin

From the perspective of the longitudinal margin, there is a difference in the lengths of the proximal and distal resection margins for colon cancer surgery (Figure 2). Some surgeons may use a margin of 10 cm or more as a sufficient longitudinal resection margin. In a Japanese study, most metastatic foci were distributed within 5 cm of the tumor; therefore, it was considered sufficient to secure a resection margin of 5 cm on both sides[65,66]. In addition, the extended longitudinal resection margin should be broadly secured because the hepatic or splenic flexure area has dual lymphatic drainage. However, many studies have shown that there is no significant difference in the therapeutic effects of conventional radical resection and extended radical resection in colon cancer surgery[67-70].

Therefore, maintaining the intact mesocolic plane is accepted as an important factor, but a resection margin greater than 10 cm from the primary tumor can be considered selectively depending on the location and stage of the tumor, its relationship to the feeding vessel, and the spread of lymph node metastasis.

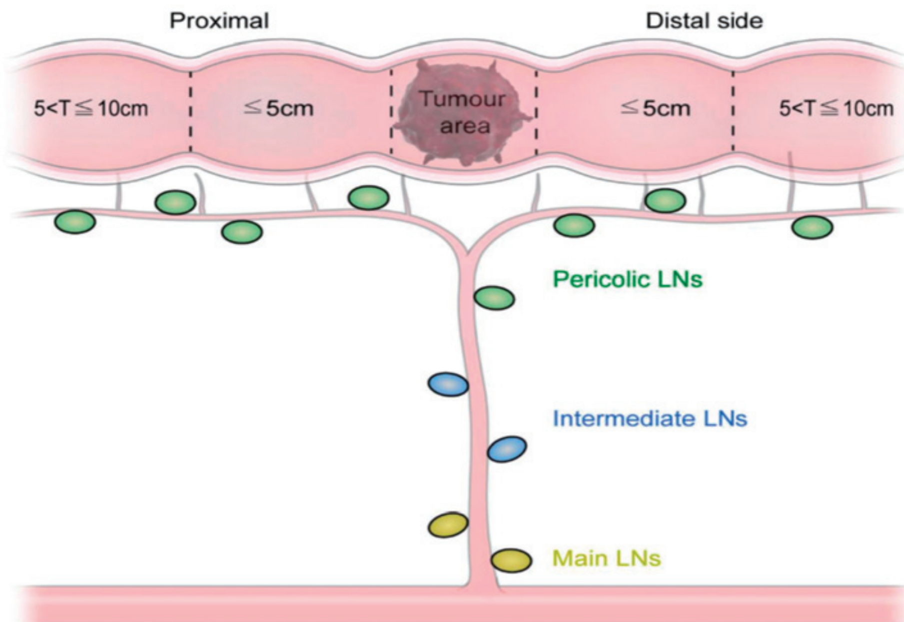

Figure 2. Grouping of the retrieved lymph nodes. Adapted from Yang et al. [62], according to the Creative Commons License of open access.

Novel Technology of Lymph Node Mapping

Recently, fluorescence lymph node mapping has been developed as a promising image-guidance technique. When indocyanine green (ICG) is injected into the colonic wall as a fluorescent dye, it enters the lymphatic system from the perivascular space[71]. In colon cancer surgery, fluorescence lymph node mapping could help visualize the lymphatic pathway for accurate and safe lymph node dissection, especially around the main surgical trunk (Figure 3). The fluorescence lymph node mapping technique can increase the number of harvested lymph nodes[72,73]. When visualizing the lymph nodes and lymphatic drainage pathway directly, the surgeon can easily dissect the lymph nodes related to the primary tumor. Retrieving an adequate number of lymph nodes is essential for accurate pathological staging. From an oncological point of view, at least 12 lymph nodes should be retrieved to evaluate the pathological stage so that patients can receive appropriate chemotherapy after surgery. The fluorescence lymph node mapping procedure improved the rate of harvesting more than 12 lymph nodes[74].

Sentinel lymph node resection is an established technique for breast cancer and malignant melanoma to reduce postoperative complications related to radical resection. The sentinel lymph node is the site of initial drainage of hypothetical lymph nodes from the primary cancer. Radioisotopes, blue dyes, and fluorescence dyes are used for lymph node mapping[75]. With the development of near-infrared camera systems, fluorescence lymph node mapping has been adopted for detecting sentinel lymph nodes in laparoscopic and robotic colon cancer surgery. The success rate of lymph node mapping was >90% through colonoscopic submucosal injection of the optimal ICG dosage[74]. Sentinel lymph node mapping is a preliminary procedure for determining radical or selective lymph node dissection. In colon cancer, lymphatic flow can spread to various routes through a complex lymphatic network rather than through a linear connection. To date, sentinel lymph node mapping has many limitations in assessing lymph node metastasis[76]. Many questions are yet to be answered, but further advances in fluorescence dyes and imaging devices would accelerate the improvement of fluorescence lymph node mapping and enable the determination of the expansion of radical lymphadenectomy, especially in early colon cancer[77].

Conclusion

To determine the optimal treatment for early colon cancer, it is essential to evaluate the risk factors for lymph node metastasis through endoscopic optical assessments and pathological evaluation. A multidisciplinary approach should be recommended to establish an optimized treatment strategy, minimize the risk of complications, and obtain excellent oncologic outcomes via patient-tailored treatment in patients with early colon cancer.

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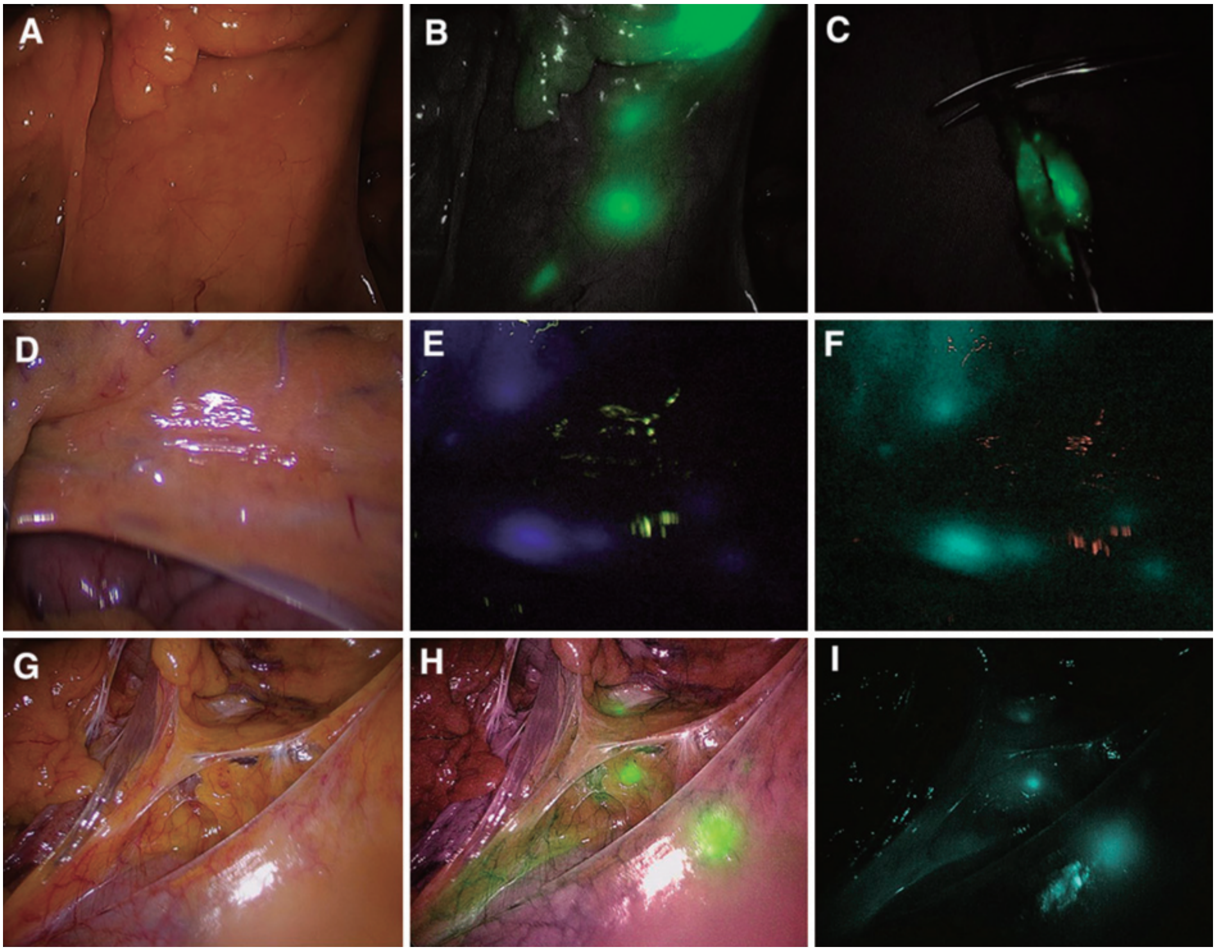

Figure 3. Fluorescence lymph node mapping (FLNM) using laparoscopic near-infrared camera systems: Stryker (1588 AIM camera system; Stryker, USA) (A–C), Storz (IMAGE1 S^{TM}; Karl Storz, Germany) (D–F), and Olympus (CLV-S200-IR; Olympus, Japan) (G–I). (A), (D), and (G) show the mesentery of the colon under white light. Green fluorescence-colored lymph nodes are seen using the Endoscopic Near-Infrared Visualization (ENV) mode of the Stryker (B). Isolating the indocyanine green (ICG)-dyed lymph nodes from the specimen, which is fully resected from the surgical field (C). Blue-colored lymph nodes are seen under the conventional ICG mode (E) and green-colored under the Spectra mode (F) of the Storz. Partial white light and infrared (IR) light at the same time lead to green-colored lymph nodes overlapping with original view as seen in the narrow-band imaging (NBI) mode (H) of the Olympus; green-colored lymph nodes are seen in the IR mode (I). Adapted from Ahn et al. [74], according to the Creative Commons License of open access.

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Conflicts of Interest
There are no conflicts of interest.

Author Contributions
Gyung Mo Son: conception and design of the study, drafting and revising the study, final approval of the version to be submitted for publication
Su Bum Park: conception of the study, revising the study, final approval of the version to be submitted for publication
Tae Un Kim: conception of the study, revising the study, final approval of the version to be submitted for publication
Byung-Soo Park: conception of the study, revising the study, final approval of the version to be submitted for publication
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Dong Hoon Shin: conception of the study, revising the study, final approval of the version to be submitted for publication

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Sung Hwan Cho: conception of the study, revising the study, final approval of the version to be submitted for publication

Hyun Sung Kim: conception of the study, revising the study, final approval of the version to be submitted for publication

Hyung Wook Kim: conception of the study, revising the study, final approval of the version to be submitted for publication

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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