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Surveillance and Characteristics of Recurrence After Curative Resection for Colorectal Cancer

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1. Introduction

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries.1 In developed counties, colorectal cancer is the second leading cause of cancer death in men and the third leading cause of cancer death in women.2 In developing countries, colorectal cancer is the fifth leading cause of cancer death in men and the sixth in women. Worldwide, colorectal cancer is the fourth leading cause of cancer death in men and the third in women.2

The most promising treatment for colorectal cancer is curative surgery. However, some patients recur after curative resection.3 In order to detect and treat recurrent tumors earlier, a post-operative surveillance after curative resection for colorectal cancer is in clinical use, although an optimal surveillance system for patients with curative resection for colorectal cancer is still uncertain.

In this chapter, we describe some topics concerning surveillance and characteristics of recurrence after curative resection for colorectal cancer as follows:

i. historical review of surveillance
ii. characteristics of recurrence
iii. surveillance tools
iv. recommended surveillance from European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and Japanese Society for Cancer of the Colon and Rectum (JSCCR)

2. Historical review of surveillance after curative resection for colorectal cancer

2.1 Randomized controlled study

The consensus on the optimal surveillance schedule after curative resection for colorectal cancer has not been established. Six randomized controlled trials (RCT) were reported to validate the usefulness of intensive surveillance after curative resection for colorectal cancer (Table 1).4-9 In all RCTs, there were no differences in recurrence rate between patients with
and without intensive follow-up. There was a description of time to recurrence after curative resection for colorectal cancer in three RCTs.\textsuperscript{4,5,7} Intensive surveillance led to earlier detection of recurrence in all three RCTs. As for curative resection rates of recurrent tumor, in three RCTs, intensive surveillance led to more frequent curative resection for recurrent tumor.\textsuperscript{4,7,9} On the other hand, in two RCTs, there were no differences in resection rates of recurrent tumor.\textsuperscript{5,6} Two RCTs disclosed the better survival in the intensive group.\textsuperscript{7,9} although the majority of RCTs failed to show a survival benefit of intensive surveillance after curative resection for colorectal cancer.\textsuperscript{4,6,8}

2.2 Meta-analysis

Although six RCTs have been conducted, all trials were underpowered or unsatisfactory. Therefore, three meta-analyses using the data of these RCTs evaluated the usefulness of intensive surveillance.\textsuperscript{10-12} There was no significant difference in recurrence rate between patients with intensive surveillance and those with non-intensive one. Renehan et al. reported that intensive surveillance led to earlier detection of recurrence after curative resection for colorectal cancer.\textsuperscript{12} Jeffery et al. clarified that intensive surveillance led to higher resection rate of recurrent tumor.\textsuperscript{11} In all meta-analyses, intensive surveillance improved survival after curative resection for colorectal cancer.

3. Characteristics of recurrence after curative resection for colorectal cancer

The Japanese Society for Cancer of the Colon and Rectum (JSCCR) organized the study group on post-surgical surveillance after curative resection for colorectal cancer in 2003. The data were collected from 14 institutions which were the members of JSCCR. The recurrence rate after curative resection for colorectal cancer was investigated according to the TNM stage and the recurrence site.\textsuperscript{3} The data of 5,230 patients who underwent curative resection for colorectal cancer from 1991 to 1996 were collected. Among 5,230 patients, 3,583 had colon cancer and 1,647 had rectal cancer. Among these, 906 patients (17.3\%) developed a recurrence during the median surveillance of 6.6 years. The characteristics of patients are shown in Table 2. The recurrence rate was significantly higher in patients with rectal cancer (24.3\%) than in those with colon cancer (14.1\%, \(p<0.0001\)).

3.1 Recurrence by TNM stage

The recurrence rate in each stage was 3.7\% in stage I, 13.3\% in stage II, and 30.8\% in stage III, respectively (\(p<0.0001\)). In each stage, the recurrence rate in patients with rectal cancer was higher than that in patients with colon cancer. The recurrence rates after curative resection for stage I, II, and III colon cancer were 2.7\%, 12.1\%, and 24.3\%, respectively. Those after curative resection for stage I, II, and III rectal cancer were 5.7\%, 16.7\%, and 43.2\%, respectively. The speed of recurrence in patients with stage I cancer was slow and constant (Figure 1a). On the other hand, the recurrence appeared rapidly within 3 years after curative resection for stage II and III colorectal cancer (Figure 1b and 1c). The cumulative appearance rates of recurrence at 3 years for stage I, II, and III were 68.6\%, 76.9\%, and 87.0\%, respectively. Those at 5 years were 96.1\%, 92.9\%, and 97.8\%, respectively. Recurrence after 5 years was rare for all three stages: 0.14\% (2/1367), 0.94\% (18/1912), and 0.67\% (13/1951), respectively.
| Author          | Year | Number of patients | Study design | Recurrence rate | Time to detection of recurrence | Resection |
|-----------------|------|--------------------|--------------|-----------------|---------------------------------|-----------|
| Kleibn et al.   | 1997 | 597                | RCT          | 26% : 26% (NS)  | 18 months : 27 months (p<0.01) | 20%       |
| Makela et al.   | 1995 | 106                | RCT          | 42% : 39% (NS)  | 10 months : 15 months (p = 0.002) | 22%       |
| Olsson et al.   | 1995 | 107                | RCT          | 32% : 33% (NS)  | -                               | 29%       |
| Pietra et al.   | 1998 | 207                | RCT          | Local recurrence 25% : 19% (NS) | Local recurrence 10 months : 20 months (p=0.0003) | 65%       |
| Schoemaker et al. | 1998 | 325                | RCT          | 34% : 41% (NS)  | -                               | -         |
| Secco et al.    | 2002 | 358                | RCT          | 53% : 57%       | -                               | 31%       |
| Figueiredo et al. | 2003 | 1679               | Meta-analysis | NS              | -                               | -         |
| Jeffery et al.  | 2002 | 1342               | Meta-analysis | Odds ratio 0.91 (NS) | -                               | -         |
| Ramoohan et al. | 2002 | 1342               | Meta-analysis | 32% : 33% (NS)  | 8.5 months earlier in intensive group (p=0.001) | -         |
Table 2. Characteristics of patients

| Characteristics                  | Patients with relapse (%) | Patients without relapse (%) | Total | P value* |
|----------------------------------|---------------------------|------------------------------|-------|----------|
| Number of patients               | 906 (17.3)                | 4324 (82.7)                  | 5230  |          |
| Age                              | 62 ± 11                   | 63 ± 11                      | 63 ± 11 | NS**     |
| Gender                           | Male 559 (18.0)           | 2546 (82.0)                  | 3105  | NS***    |
|                                  | Female 347 (16.3)         | 1778 (83.7)                  | 2125  |          |
| Primary tumor site               | Colon 506 (14.1)          | 3077 (85.9)                  | 3583  | p<0.0001*** |
|                                  | Rectum 400 (24.3)         | 1247 (75.7)                  | 1647  |          |
| TNM stage                        | Stage I 51 (3.7)          | 1316 (96.3)                  | 1367  |          |
|                                  | Stage II 255 (13.3)       | 1657 (86.7)                  | 1912  | p<0.0001*** |
|                                  | Stage III 600 (30.8)      | 1351 (69.2)                  | 1951  |          |
|                                  | Median follow-up period   | 3.5 ± 2.9                    | 7.1 ± 3.1 | p<0.0001** |

* Characteristics of patients with relapse compared to those without relapse, **Man-Whitney U test, ***chi-square test.

Fig. 1a. The cumulative appearance rate of recurrence after curative resection for stage I (a), stage II (b), and stage III (c) colorectal cancer.

Fig. 1b. The cumulative appearance rate of recurrence after curative resection for stage I (a), stage II (b), and stage III (c) colorectal cancer.
An intensive surveillance program could be adopted in stage II and III patients for the first 3 years and less intensive program for the next 2 years. Patients with stage I colorectal cancer could be followed less intensively.

### 3.2 First recurrence site

A study using autopsy reported that the most frequent metastatic site from colorectal cancer was the liver followed by the lung. This was consistent with our study (Table 3). The liver was the most frequent recurrent site after curative resection for colon cancer (7.0%). The second was the lung (3.5%). The local recurrence was most frequent after curative resection for rectal cancer (8.8%). The lung and the liver were the second and the third frequent metastatic sites. There was no difference in hepatic recurrence rate between patients with colon cancer and those with rectal cancer, while the pulmonary, local and anastomotic recurrence rates after curative resection for rectal cancer were significantly higher than those for colon cancer. In each recurrent site, approximately 80 to 90% of recurrence developed within 3 years (Figure 2). More than 95% of anastomotic recurrence was found within 3 years after curative resection for colorectal cancer (Figure 2d). In 5 years after curative resection for colorectal cancer, more than 95% of recurrence was found in each recurrent site (Table 4).

In this study, there was no patient with preoperative radiotherapy for rectal cancer. At present, the standard therapy for rectal cancer is total mesorectal excision with preoperative chemoradiotherapy in many countries. Six percent of the patients with preoperative combined modality therapy for rectal cancer followed by total mesorectal excision developed a recurrence over 5 years. In their study, of the 67 patients who developed recurrent disease, 4 (6%) had recurrent disease documented greater than 5 years following surgery. Three of these 4 patients had a distant recurrence, and 1 had both a local and distant recurrence. The recurrences were documented 61, 71, 76, and 96 months following curative rectal resection.

Therefore, the surveillance after 5 years might be necessary if patients receive radiotherapy or adjuvant chemotherapy.
Table 3. Comparison of recurrence rates between patients with colon cancer and those with rectal cancer

| First recurrence site | % recurrence (observed recurrences /5230) | Cumulative appearance rate of recurrence (%) within 3 years | within 4 years | within 5 years |
|-----------------------|------------------------------------------|---------------------------------|----------------|----------------|
| Liver                 | 7.1 (373)                                | 87.9                            | 94.1           | 98.7           |
| Lung                  | 4.8 (250)                                | 77.7                            | 88.8           | 94.8           |
| Local                 | 4.0 (209)                                | 81.1                            | 90.3           | 96.1           |
| Anastomatic           | 0.4 (22)                                 | 95.5                            | 95.5           | 95.5           |
| Others                | 3.8 (199)                                | 79.8                            | 91.4           | 95.5           |

Table 4. Recurrence rates by the initial recurrence site

Fig. 2a. The cumulative appearance rate of recurrence in liver (a), lung (b), local (c), anastomosis (d), and others (e).
Fig. 2b. The cumulative appearance rate of recurrence in liver (a), lung (b), local (c), anastomosis (d), and others (e).

Fig. 2c. The cumulative appearance rate of recurrence in liver (a), lung (b), local (c), anastomosis (d), and others (e).

Fig. 2d. The cumulative appearance rate of recurrence in liver (a), lung (b), local (c), anastomosis (d), and others (e).
3.3 Survival

According to the Japanese data, the 5-year overall survival rates in patients with stage I, II, and III colon cancer were 92.8%, 85.5%, and 76.2%, respectively (Figure 3a). Those in patients with stage I, II, and III rectal cancer were 92.2%, 84.6%, and 62.0%, respectively (Figure 3b). These outcomes seem to be better than those of the patients in the Surveillance, Epidemiology, and End Results (SEER) population-based data from 1992 to 2004. According to the SEER data, the 5-year survival rates in patients with stage I, T3N0, and T4N0 colon cancer were 76.3%, 66.7%, and 55.0%, respectively. Those in patients with stage III colon cancer varied from 73.7% (T1-2N1a) to 12.9% (T4bN2b).

Fig. 3a. The overall survival curve after curative resection for cancer of the colon (a) and rectum (b).
In terms of rectal cancer, the 5-year overall survival rates in Japanese patients with stage I, II, and III rectal cancer were 92.2%, 84.6%, and 62.0%, respectively. According to the SEER data, the 5-year observed survival rates in patients with stage I, T3N0, and T4N0 rectal cancer were 77.6%, 64.0%, and 50.5%, respectively. As for stage III rectal cancer, the 5-year observed survival rates varied from 75.7% (T1N1a) to 12.3% (T4bN2b).

In each stage, the prognosis of the Japanese patients with colorectal cancer was better than that of US patients. One of the possible reasons might be the difference of surveillance system after curative resection for colorectal cancer. The Japanese patients with curative resection for colorectal cancer usually receive more intensive surveillance to detect recurrence than the American patients. Another possible reason might be the difference of surgical technique. The Japanese surgeons usually perform central vascular ligation to dissect regional lymph node. Some European institutions adopt the similar technique called complete mesocolic excision with central ligation. Hohenberger et al. presented an excellent outcome of patients who underwent complete mesocolic excision with central ligation. However, most institutions in the Western countries do not adopt this technique.

### 3.4 Resection for recurrence

In our study, among the 906 patients with recurrence after curative resection for colorectal cancer, 379 (41.8%) underwent resection for recurrence with curative intent. The prognoses of patients with resection for recurrence were better than those without resection. The 5-year survival rates after initial colorectal surgery in patients with and without resection for hepatic, pulmonary, local, and anastomotic recurrence were 55% and 11% (p<0.0001), 68% and 13% (p<0.0001), 48% and 22% (P = 0.0002), and 53% and 0% (p = 0.0003), respectively (Figure 4). The 5-year survival rates after resection for hepatic, pulmonary, local, and anastomotic recurrence were 45%, 48%, 27%, and 33%, respectively.
Fig. 4a. The outcomes after initial colorectal surgery in patients with and without resection for recurrence of liver (A), lung (B), local (C), and anastomosis (D).

Liver (n = 373)

Lung (n = 250)

Fig. 4b. The outcomes after initial colorectal surgery in patients with and without resection for recurrence of liver (A), lung (B), local (C), and anastomosis (D).
Fig. 4c. The outcomes after initial colorectal surgery in patients with and without resection for recurrence of liver (A), lung (B), local (C), and anastomosis (D).

Fig. 4d. The outcomes after initial colorectal surgery in patients with and without resection for recurrence of liver (A), lung (B), local (C), and anastomosis (D).
3.5 Timing of recurrence

Patients were classified into three groups according to the timing of recurrence (TR): TR ≤ 1 year, 1 < TR ≤ 3 years, 3 years < TR. The earlier the hepatic, pulmonary, and local recurrence, the poorer the survival after initial colorectal surgery (Figure 5). If patients had resection for recurrence, there was no difference in survival after recurrence according to the timing of recurrence (Figure 6).

Fig. 5a. The overall survival curve after initial colorectal surgery according to the timing of recurrence. The later recurrence in liver (a), lung (b), and local (c) leads to the better survival.

Fig. 5b. The overall survival curve after initial colorectal surgery according to the timing of recurrence. The later recurrence in liver (a), lung (b), and local (c) leads to the better survival.
Fig. 5c. The overall survival curve after initial colorectal surgery according to the timing of recurrence. The later recurrence in liver (a), lung (b), and local (c) leads to the better survival.

Fig. 5d. The overall survival curve after initial colorectal surgery according to the timing of recurrence. The later recurrence in liver (a), lung (b), and local (c) leads to the better survival.
Fig. 6a. If the patients underwent curative resection for recurrence, the outcomes after recurrence were irrespective of the timing of recurrence.

Fig. 6b. If the patients underwent curative resection for recurrence, the outcomes after recurrence were irrespective of the timing of recurrence.
4. Surveillance tools after curative resection for colorectal cancer

In our study, the combination of symptoms, physical examination, and tumor marker detected the majority of recurrence in all sites except for lung (Table 5). In this section, the evidence for usefulness of each surveillance tool is discussed.
Table 5. Rate of first indicator for recurrence

| First indicator | Rate of recurrence |
|-----------------|--------------------|
| Abdominal pain  | 46.6%              |
| Anal bleeding   | 51.5%              |
| Anal pain       | 41.4%              |
| C. Tumor marker | 46.4%              |
| A × B = C       | 26.4%              |
| Local (in = 200) | 34.8%              |
| Limit (in = 375) | 24.8%              |
| Rate of Fi* (%) | 27.2%              |

*FI: First indicator
**Symptoms include anal pain, anal bleeding, abdominal pain, and so on
***CS: Colonoscopy

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4.1 History and physical examination

It is not rare that patients have a symptom at the time of recurrence after curative resection for colorectal cancer. According to the result of RCTs, 16% to 66% of patients had some sort of symptom. Therefore, periodical clinical visits seem to be important to detect a recurrence after curative resection for colorectal cancer. On the other hand, Ohlsson et al. reported that it was rare to detect a resectable recurrent tumor only history and physical examination.

4.2 CEA

Carcinoembryonic antigen (CEA) is most widely used as tumor marker for colorectal cancer. The serum CEA level was high in the majority of patients with recurrence after curative resection for colorectal cancer. Especially, 80% of patients with hepatic recurrence from colorectal cancer had higher serum CEA levels. Graham et al. reported that serum CEA measurement was the most useful and economical surveillance tool to detect recurrence after curative resection for colorectal cancer. Therefore, serum CEA test was recommended as a surveillance tool after curative resection for colorectal cancer.

4.3 Chest X-ray

It is controversial to use chest x-ray as a surveillance tool to detect recurrence after curative resection for colorectal cancer. Since chest x-ray can detect resectable pulmonary metastasis with probability of 1%, it is not recommended to use chest x-ray as a surveillance tool in many institutions. On the other hand, Ike et al. reported the good outcomes of 42 patients with curative resection for pulmonary recurrence which was detected by the combination of serum CEA test of every 2 months and chest x-ray of every 6 months. The 5-year survival rate after curative resection for pulmonary recurrence was 63.7%.

4.4 CT scans

Howell et al. reported that annual computed tomography (CT) scan could detect 87.5% of liver metastases at an asymptomatic stage, whereas, in total, only 2 cases out of 157 (1.3%) underwent curative resection for liver metastases. An RCT conducted by Schoemaker et al. clarified that abdominal CT scan increased the detection rate of liver metastases, although there was no difference in resection rate between the groups with and without CT scan. On the other hand, the UK group reported the usefulness of serum CEA measurement and CT scan in the surveillance of patients after adjuvant chemotherapy for colorectal cancer. In their study, among 530 patients with stage II and III colorectal cancer, 154 had recurrence after adjuvant chemotherapy. Recurrences were detected by symptoms (n = 65), CEA (n = 45), CT (n = 49), and others (n = 9). The CT-detected group had a better survival compared with the symptomatic group (P = .0046).

Intensive surveillance after curative resection for colorectal cancer was not adopted in Western countries. However, since the results of meta-analyses revealed that intensive surveillance after curative resection for colorectal cancer contributed to better outcomes, routine use of CT scans has been recommended.

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4.5 PET scans

The usefulness of positron-emission tomography (PET) in the detection of recurrence after curative resection for colorectal cancer is uncertain. Sobhani et al. reported a clinical trial that randomly assigned 130 patients with curative resection for colorectal cancer to the conventional surveillance group (periodic serum tumor marker, ultrasound, chest x-ray, and CT scans) and the PET-additional group. The PET scans were performed in 9 and 15 months after surgery. Recurrences were detected after a shorter time (12.1 vs 15.4 months) in the PET group. Moreover, recurrences were more frequently cured by surgery (R0) in the PET group. The usefulness of PET scans in the detection of recurrence after curative resection for colorectal cancer should be clarified in a large-scale study.

4.6 Colonoscopy

Since the anastomotic recurrence rate after colectomy is low, the usefulness of periodical colonoscopy to detect anastomotic recurrence is skeptical. On the other hand, since the anastomotic recurrence rate after resection for rectal cancer is higher than that after resection for colon cancer, several studies reported the adequacy of periodical colonoscopy to detect anastomotic recurrence after surgery. At the same time, colonoscopy can find metachronous adenoma and cancer in the colon and rectum. Metachronous lesions develop in 1.5 to 3% of patients in the first 5 years after colorectal surgery. In Japan, the colonoscopy is usually performed one year after colorectal surgery and thereafter every two years. If total colonoscopy cannot be performed preoperatively because of the stenosis, it is recommended that the first colonoscopy should be performed three to six months after colorectal surgery.

5. Recommended surveillance after curative resection for colorectal cancer from ESMO, ASCO, and JSCCR

Both previous and present guidelines for surveillance after curative resection for colorectal cancer from ASCO and ESMO are shown in Table 6. Previously, neither ASCO nor ESMO recommended the intensive surveillance after curative resection for colorectal cancer, because most RCTs failed to show the prognostic significance of intensive surveillance. However, since three meta-analyses showed the effectiveness of intensive surveillance, these guidelines changed their attitude toward surveillance after curative resection for colorectal cancer. At present, both societies recommend periodical serum CEA measurement and CT. Periodical colonoscopy to detect metachronous adenoma and cancer is also recommended.

In Japan, JSCCR published the first edition of guidelines for the treatment of colorectal cancer in 2005 and the second edition in 2009. The Japanese institutions adopted more intensive surveillance to detect recurrence after curative resection for colorectal cancer. The recommended surveillance schedule in the Japanese guidelines is shown in the Table 7.

On the other hand, the optimal schedule and modality to detect recurrence after curative resection for colorectal cancer are still uncertain. These issues should be clarified by RCTs in future.
| Table 6. Recommended guidelines from ASCO and ESMO |
|---------------------------------------------------|
| **ASCO**                                         |
| **Previous**                                     |
| **Present**                                      |
| **ASCO**                                         |
| **Previous**                                     |
| **History and physical examination**              | Every 3 to 6 months for the first 3 years and annually thereafter | Every 3 to 6 months for the first 3 years, every 6 months during years 4 and 5, and subsequently at the discretion of the physician | Every 6 months for 2 years |
| **Carcinoembryonic antigen**                      | If resection of liver metastases would be clinically indicated, it is recommended that postoperative serum CEA testing be performed every 2 to 3 months in patients with stage II or III disease for ≤ 2 years after diagnosis. | Every 3 months postoperatively for at least 3 years after diagnosis, if the patient is a candidate for surgery or systemic therapy | Restricted to patients with suspicious metastases |
| **Chest x-ray**                                   | May be ordered to diagnose abnormalities prompted by elevated CEA levels or for patients who have symptoms suggestive of a pulmonary metastasis | Not recommended | Restricted to patients with suspicious metastases |
| **Chest computed tomography**                     | – | Annually for 3 years after primary therapy for patients who are at higher risk of recurrence and who could be candidates for curative-intent surgery | Restricted to patients with suspicious metastases |
| **Abdominal ultrasonography**                     | Not recommended | – | Annually for 3 years |
| **Abdominal computed tomography**                 | Not recommended | Annually for 3 years after primary therapy for patients who are at higher risk of recurrence and who could be candidates for curative-intent surgery | Restricted to patients with suspicious metastases |
| **Pelvic computed tomography**                    | Not recommended | For rectal cancer surveillance, especially for patients with several poor-prognostic factors, including those who have not been treated with radiation | Not recommended |
| **Colonoscopy**                                  | Every 3 to 5 years to detect new cancers and polyps | All 3 years after operative treatment, and, if results are normal, every 5 years thereafter; flexible proctosigmoidoscopy every 6 months for 5 years for rectal cancer patients who have not been treated with pelvic radiation | Every 5 years |
Table 7: Surveillance schedule recommended by JSCCR

| Stage | CEA and CA19-9 | Abdominal CT | Chest CT | Abdominal and pelvic CT | Colonoscopy |
|-------|-----------------|--------------|----------|------------------------|-------------|
| I     |                 |              |          |                        |             |
| II    |                 |              |          |                        |             |
| III   |                 |              |          |                        |             |

- Stage I – Stage III: Omissible in Stage I and Stage II

Stage I - Stage III
6. Summary

i. The most frequent site of recurrence after curative resection for colon cancer is the liver. The second is the lung.

ii. The most frequent site of hematogenous recurrence after curative resection for rectal cancer is the lung. The second is the liver.

iii. The recurrence rate in rectal cancer is higher than in colon cancer.

iv. Approximately 80 to 90% of recurrence after curative resection for colorectal cancer developed within 3 years.

v. In any recurrent sites, the prognosis of patients with curative resection for recurrence was better than that of patients without curative resection for recurrence.

vi. The later the recurrence, the better the survival.

vii. If patients undergo curative resection for recurrence, the prognosis after resection for recurrence is irrespective of timing of recurrence.

viii. Although the optimal surveillance tools and schedule are uncertain, the intensive surveillance leads to better survival after curative resection for colorectal cancer compared to the non-intensive one.

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