Epidemiology and prognosis of ovarian metastases in colorectal cancer

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Background: National guidelines for prophylactic oophorectomy in women with colorectal cancer are lacking. The aim of this population-based cohort study was to report on the prevalence, incidence and prognosis of ovarian metastases from colorectal cancer, providing information relevant to the discussion of prophylactic oophorectomy.

Methods: All 4566 women with colorectal cancer in Stockholm County during 1995–2006 were included and followed until 2008. Prospectively collected data regarding clinical characteristics, treatment and outcome were obtained from the Regional Quality Registry.

Results: The prevalence of ovarian metastases at the time of diagnosis of colorectal cancer was 1·1 per cent (34 of 3172) among women with colonic cancer and 0·6 per cent (8 of 1394) among those with rectal cancer (P = 0·105). After radical resection of stage I–III colorectal cancer, metachronous ovarian metastases were found during follow-up in 1·2 per cent (22 of 1971) with colonic cancer and 0·1 per cent (1 of 881) with rectal cancer (P = 0·006). Survival in patients with ovarian metastases was poor.

Conclusion: Ovarian metastases from colorectal cancer are uncommon.

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Introduction

The prevalence and incidence of ovarian metastases (OM) in colorectal cancer is not well known. Previous studies from single centres have reported synchronous OM in 0–9 per cent of women with colorectal cancer and metachronous OM in 0·9–7 per cent1–4. Population-based studies are lacking.

The role of prophylactic oophorectomy in women with colorectal cancer is not well defined. National guidelines are lacking, or based on one underpowered clinical trial and single-centre reports2,3,6. It is controversial whether the procedure should be done concurrently with other indicated non-gynaecological surgery. Prophylactic oophorectomy reduces the risk of primary ovarian cancer, removes microscopic synchronous OM and prevents the development of metachronous OM. However, in both premenopausal and postmenopausal women, oophorectomy increases the risk of hormone deficiency, with negative psychological and metabolic consequences7–11. The patient’s age, heredity for ovarian, breast and endometrial cancer, hormone status, and wishes are other important factors to consider in decision making before surgery.

The aim of this study was to analyse the clinical characteristics, prevalence and incidence of OM, and survival in women with colorectal cancer in a population of 1·9 million inhabitants, to provide information relevant to the discussion of prophylactic oophorectomy.

Methods

In Sweden it is compulsory for the treating physician and pathologist to report every new cancer diagnosis to the National Cancer Registry12. The Stockholm County Council registry covers healthcare consumption, diagnoses according to the International Classification of Diseases and type of surgery performed for all 1·9 million inhabitants in the region. Every resident of Sweden has a unique identification number that forms the basis for these registries.
In addition, since 1995 (rectal cancer) and 1996 (colonic cancer), information on all patients with colorectal cancer in Stockholm County has been reported prospectively to a Regional Quality Registry by the surgeon, pathologist and oncologist in charge. The Regional Quality Registry includes detailed clinical data on patients and tumour characteristics, treatment and follow-up. The database is validated continuously. The regional treatment programme for colorectal cancer recommends X-ray of the lungs and ultrasonography or computed tomography of the liver for the assessment of distant metastases. Since 2003, magnetic resonance imaging has been recommended for local staging of rectal cancer.

Study population and data analysis

This study included all 4566 women in Stockholm County diagnosed with colorectal cancer, without previous or synchronous history of gynaecological cancer, registered from January 1995 (rectal cancer) or January 1996 (colonic cancer) to December 2006 (Fig. 1). Gynaecological cancer diagnosed within 3 months of the colorectal cancer was defined as synchronous. Patients were followed until death or the end of follow-up (December 2008).

Data were obtained from the Regional Quality Registry and the Stockholm County Council registry. Medical records and histopathology reports were reviewed for patients who had OM, synchronous or metachronous primary ovarian cancer and for patients with missing follow-up data. Metastases diagnosed at autopsy were also included in the study.

When analysing the incidence of metachronous OM, patients who had undergone bilateral oophorectomy synchronously with the operation for the primary tumour were excluded as they were not at risk of developing OM.

Data were analysed separately for patients with colonic and rectal cancer who were potentially cured, that is patients with stage I–III colonic and rectal cancer who underwent an R0 resection (margins free from tumour) according to both the surgeon and the pathologist. Data on those with metachronous OM were presented only for women with colonic cancer as metachronous OM were very uncommon in those with rectal cancer. Patients were

![Flow chart for all women with colorectal cancer and ovarian metastases in Stockholm County, 1995–2006](image_url)
allocated to one of three groups (no recurrence, OM and any other recurrence), and data for these were analysed separately.

Prophylactic oophorectomy was defined as bilateral salpingo-oophorectomy performed synchronously with resection of the primary tumour in a patient with stage I–III colorectal cancer at the time of diagnosis.

### Statistical analysis

Distributions were compared with the $\chi^2$ test of independence or Fisher’s exact test as appropriate. Continuous variables, such as age and time, were compared with the Mann–Whitney $U$ or Kruskal–Wallis test. All tests were two sided and $P < 0.001$ was considered statistically significant. Survival was estimated using the Kaplan–Meier method and the differences were statistically significant. Survival was estimated using PASW Statistics 18.0.0 (SPSS, Chicago, Illinois, USA), except that cumulative incidences were calculated using R version 2.8.1 (R foundation for Statistical Computing, Vienna, Austria).

### Results

In all, 4799 women with colorectal cancer were included in the Regional Quality Registry during the study interval (Fig. 1). Two hundred and thirty-three patients with synchronous or previous gynaecological cancer were excluded from further analysis. Characteristics of patients in the study cohort are presented in Table 1.

Overall, synchronous and metachronous OM were more common in women with colonic cancer than in those with rectal cancer, being found in 69 (2.2 per cent) of 3172 and ten (0.7 per cent) of 1394 respectively ($P < 0.001$). The diagnosis of OM was confirmed by the histopathological results in 74 of 79 women (including one with synchronous OM diagnosed at autopsy), by computed tomography in three, by magnetic resonance imaging in one, and during surgery without a histopathological diagnosis in one patient.

The prevalence of synchronous OM at the time of diagnosis of the primary tumour was 0.9 per cent (42 of 4566) for all patients with colorectal cancer, 1.1 per cent (34 of 3172) among women with colonic cancer and 0.6 per cent (8 of 1394) among those with rectal cancer ($P = 0.105$). In nine of the 42 patients, OM were the only manifestation of disseminated disease. The estimated 5-year overall survival rate was 62.1 (60.4 to 63.8) per cent in patients with stage I–III colorectal cancer, 11 (0.4 to 21) per cent in those with synchronous OM and 3.5 (2.1 to 4.9) per cent in patients with any other synchronous metastases.

### Table 1 Patient characteristics at the time of diagnosis and treatment

<table>
<thead>
<tr>
<th></th>
<th>All patients ($n = 4566$)</th>
<th>Colonic cancer ($n = 3172$)</th>
<th>Rectal cancer ($n = 1394$)</th>
<th>$P$†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)†</td>
<td>75 (22–100)</td>
<td>76 (22–99)</td>
<td>72 (24–100)</td>
<td>&lt; 0.001;</td>
</tr>
<tr>
<td>Tumour stage</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001.</td>
</tr>
<tr>
<td>I</td>
<td>702 (15.4)</td>
<td>369 (11.6)</td>
<td>333 (23.9)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1466 (32.1)</td>
<td>1148 (36.2)</td>
<td>318 (22.8)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1236 (27.1)</td>
<td>873 (27.5)</td>
<td>363 (26.0)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>966 (21.2)</td>
<td>706 (22.3)</td>
<td>260 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>196 (4.4)</td>
<td>76 (2.4)</td>
<td>120 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Synchronous ovarian metastases</td>
<td>42 (0.9)</td>
<td>34 (1.1)</td>
<td>8 (0.6)</td>
<td>0.105</td>
</tr>
<tr>
<td>Preoperative oncolgical treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>652 (14.3)</td>
<td>11 (0.3)</td>
<td>641 (46.0)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>25 (0.5)</td>
<td>21 (0.7)</td>
<td>4 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy + chemotherapy</td>
<td>49 (1.1)</td>
<td>5 (0.2)</td>
<td>44 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Resection of primary tumour</td>
<td>3946 (86.4)</td>
<td>2815 (86.7)</td>
<td>1131 (81.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Emergency</td>
<td>752 (16.5)</td>
<td>695 (21.9)</td>
<td>57 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>3552 (77.8)</td>
<td>2311 (72.9)</td>
<td>1241 (89.0)</td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>262 (5.7)</td>
<td>166 (5.2)</td>
<td>96 (6.9)</td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †$\chi^2$ test for comparison of colonic versus rectal cancer, except ‡Mann–Whitney $U$ test.
Metachronous OM were found in 37 (0.8 per cent) of 4527 women with colorectal cancer, 35 (1.1 per cent) of 3144 with colonic cancer and two (0.1 per cent) of 1383 with rectal cancer ($P < 0.001$). None of the patients with colorectal cancer who developed metachronous OM had previously undergone radiotherapy for the colorectal cancer.

During follow-up, metachronous primary ovarian cancer and cancer of the uterine cervix and corpus were diagnosed in 31 and three patients respectively. Six of the patients with cancer of the uterine cervix and corpus had previously had radiotherapy for rectal cancer.

Among patients with potentially cured colorectal cancer (those who had undergone R0 resection of stage I–III disease), metachronous OM were found in 22 (1.1 per cent) of 1971 patients with colonic cancer and one (0.1 per cent) of 881 with rectal cancer ($P = 0.006$). The OM were diagnosed a median of 16 (range 2–50) months after resection of the primary tumour. Among women with colonic cancer, patients who developed OM were younger than those with any other recurrence or no recurrence ($P < 0.001$) (Table 2). Tumour stage was more advanced and emergency surgery was more common in the OM group than in the other two groups ($P < 0.001$).

Isolated OM were diagnosed in only seven of the 22 patients after R0 resection of stage I–III colonic tumours. The remaining 15 patients had metastases diagnosed at least one other location before or at the same time as the OM, peritoneal carcinomatosis being the most common finding. The 5-year cumulative incidence of metachronous ovarian metastases and other recurrences is shown in Fig. 2.

Survival in the OM group was as poor as that among patients with other recurrences, with estimated 5-year overall survival rates of 22 (4 to 40) and 16.5 (11.9 to 21.0) per cent respectively (Fig. 3).

Unilateral oophorectomy was performed in 22 (0.5 per cent) and bilateral oophorectomy in 60 (1.3 per cent) of 4566 patients with colorectal cancer during the study interval. Sixty-nine of these had OM, three had direct overgrowth of the primary colorectal cancer, and ten had no pathology in the ovaries but either distant metastases at other sites (7) or a suspicion of ovarian involvement (3). No

Table 2 Characteristics at the time of diagnosis of patients who underwent R0 resection of stage I–III colonic cancer, grouped according to recurrence

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No recurrence (n = 1655)</th>
<th>Metachronous ovarian metastases (n = 22)</th>
<th>Any other recurrence (n = 294)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>76 (24–97)</td>
<td>62.5 (22–84)</td>
<td>74 (25–94)</td>
<td>&lt; 0.001‡</td>
</tr>
<tr>
<td>Tumour location</td>
<td></td>
<td></td>
<td></td>
<td>0.320</td>
</tr>
<tr>
<td>Right colon</td>
<td>830 (50.2)</td>
<td>12 (55)</td>
<td>139 (47.3)</td>
<td></td>
</tr>
<tr>
<td>Transverse colon</td>
<td>170 (10.3)</td>
<td>3 (14)</td>
<td>22 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Left colon</td>
<td>654 (39.5)</td>
<td>7 (32)</td>
<td>133 (45.2)</td>
<td></td>
</tr>
<tr>
<td>Colon, NOS</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Tumour stage</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>I</td>
<td>334 (20.2)</td>
<td>0 (0)</td>
<td>14 (4.8)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>876 (52.9)</td>
<td>8 (36)</td>
<td>97 (33.0)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>445 (26.9)</td>
<td>14 (64)</td>
<td>183 (62.2)</td>
<td></td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Emergency</td>
<td>255 (15.4)</td>
<td>8 (36)</td>
<td>80 (27.2)</td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>1400 (84.6)</td>
<td>14 (64)</td>
<td>214 (72.8)</td>
<td></td>
</tr>
<tr>
<td>Time from resection of primary tumour to death or end of follow-up (months)*</td>
<td>83 (0–155)</td>
<td>96 (16–107)</td>
<td>92 (2–126)</td>
<td>0.062‡</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages unless indicated otherwise; *values are median (range). NOS, not otherwise specified. ‡$\chi^2$ test, except †Mann–Whitney $U$ test.
In this population-based study, OM were uncommon in women with colorectal cancer. Synchronous and metachronous OM occurred more frequently in patients with colonic cancer than in those with rectal cancer. Patients with colonic cancer who developed OM were younger, had a more advanced tumour stage and more often underwent emergency surgery for the primary tumour than those without a recurrent malignancy during follow-up. Among women with colonic cancer, survival of those who developed metachronous OM was as poor as that of patients with other recurrence.

Earlier single-centre studies reported synchronous OM in 0–9 per cent of women with colorectal cancer and metachronous OM in 0.9–7 per cent. In the present population-based study, the prevalence was only 0.9 per cent for synchronous OM and the cumulative incidence of metachronous OM during follow-up was 0.8 per cent. This is probably not a result of underreporting as thorough review of the registers and medical records probably identified most diagnosed OM. Nevertheless, asymptomatic OM may have been underdiagnosed because the intensity of follow-up varied during the study period. In addition, the autopsy rate was low during the study interval.

OM were more commonly associated with colonic than rectal cancer. One reason for this could be that carcinomatosis, with an increased risk of peritoneal spread to the ovaries, is more common in patients with colonic cancer than in those with rectal cancer. Another contributing factor could be that nearly half of the women with rectal cancer were treated with radiotherapy. The effect of preoperative radiotherapy on the ovaries is unclear in women with rectal cancer. It is possible that radiotherapy itself eradicates micrometastases in the ovaries, but also causes ovarian atrophy and impairs the ovarian blood supply, thereby reducing the risk of haematogenous spread of the colorectal cancer to the ovaries.

The impact of radiotherapy for rectal cancer as a risk factor for second cancers has been analysed in some studies, but the results are inconclusive. Birgisson and colleagues reported an increased risk of second malignancies mainly within or adjacent to the irradiated volume. Kendal and co-workers reported no increased risk when all second cancers were considered together, but a decreased risk of cancer of the prostate and an increased risk of cancer of the uterine cervix and corpus when risks of specific cancers were analysed separately. No increased risk for primary ovarian cancer was seen in either of these investigations. In the present study, none of the patients treated with radiotherapy for colorectal cancer developed primary ovarian cancer during follow-up.

Only 1–1 per cent of patients with stage I–III colonic cancer who underwent R0 resection developed metachronous OM during follow-up. These patients were younger than those developing any other recurrence, which may be a result of a decreasing risk of haematogenous tumour spread to atrophic ovaries in older women. This is in accordance with other studies reporting an even lower median age in women developing OM from colorectal cancer.

Patients diagnosed with metachronous OM were younger than those with other recurrences, but survival was equally poor in both groups. This may indicate that the development of OM is a sign of more aggressive disease or that OM are diagnosed late in the cancer disease process.

The risk of primary ovarian cancer is increased in women with hereditary non-polyposis colorectal cancer syndrome and breast–ovarian cancer syndrome (BRCA1/2 mutation). In these patients, prophylactic oophorectomy is an important component of ovarian cancer risk reduction. In the discussion regarding prophylactic oophorectomy, it is of value to have knowledge of the risk of developing metachronous OM. This study shows that metachronous OM from colorectal cancer are uncommon, and this does not favour routine prophylactic oophorectomy. More important factors to consider before surgery are the patient’s age, individual factors, and the familial risk.
risk of primary ovarian, breast and endometrial cancer, desire to preserve hormone status and, not least, her own wishes.

Acknowledgements

The authors thank Tongplaew Singnomklao for help with data collection. Financial support was provided through the Regional Agreement on Medical Training and Clinical Research (ALF) between Stockholm County Council and the Karolinska Institute. The study was also supported by the Swedish Cancer Society, the Stockholm Cancer Society and the Bengt Ihre Foundation. The authors declare no conflict of interest.

References

**Spotlight on the colon**

1 – 5 December 2019, St. Gallen, Switzerland

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**Sunday, 1 Dec. 2019**

**MASTERCLASS**

09.00 When the appendix plays nasty: intraoperative surprises, immediate solutions, and long-term treatment options
Justin Davies, Cambridge, UK

09.40 All the secrets of the pelvic floor—common disorders and proven solutions
Julie Cornish, Cardiff, UK

10.20 M2 in 2020 – when the dust settles: current and innovative indications, implementation, and practical advice
Roo Hopley, Amsterdam, NL

11.30 Complete mesocolic excision: indications, surgical approaches, and pitfalls
Paris Tekkis, London, UK

12.10 The views of an Editor and the wisdom of an Expert: contemporary publications with the potential to change and improve practice
Neil Mortensen, Oxford, UK

14.00 To customise or not and when? The value and downside of a diverting stoma versus stoma ileostomy versus no stoma
Gabriela Möslin, Wuppertal, DE

14.40 Extended lymph node dissection: indications, surgical anatomy, and technical approaches
Peter Sagar, Leeds, UK

15.20 Is the longer the new better—how to safely extend the interval after neoadjuvant chemoradiotherapy prior to surgery for rectal cancer
Ronan O’Connell, Dublin, IE

16.30 The colorectal anastomosis: time-proven wisdom, innovative configurations, and salvage techniques
André d’Hoore, Leuven, BE

17.10 All you need to know about stomas but never dared to ask
Willem Bemelman, Amsterdam, NL

17.50 The EBSCO Coloproctology Examination
Michel Adamin, Winterthur, CH

18.00 Wrap-up
Michel Adamin, Winterthur, CH

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**Monday, 2 Dec. 2019**

**SCIENTIFIC PROGRAMME**

09.45 Opening and welcome
Jochen Lange, St. Gallen, CH

10.00 Pathophysiology and non-operative management of symptomatic uncomplicated diverticular disease
Robin Spiller, Nottingham, UK

10.40 Surgery of acute diverticulitis – evidence, eminence and real life
Willem Bemelman, Amsterdam, NL

11.00 Management of atypical diverticulitis
Dieter Hahnloser, Lausanne, CH

11.30 Hartmann reversal: open, laparoscopic or transanal?
Roo Hopley, Amsterdam, NL

13.30 The surgeon personality – influence on decision making, risk taking and outcomes
Desmond Winter, Dublin, IE

14.00 SATELLITE SYMPOSIUM Medtronic

15.00 Clinical applications of image-guided cancer surgery
Cornelis van de Velde, Leiden, NL

16.00 Volvulus of the colon – a treatment algorithm
Peter Sagar, Leeds, UK

16.30 Hereditary colorectal cancer syndromes: tailored surgical treatment
Gabriela Möslin, Wuppertal, DE

17.00 Lars Pahlman Lecture

**Tuesday, 3 Dec. 2019**

09.00 Robotic-assisted versus conventional laparoscopic surgery for rectal cancer
Amjad Parvaiz, Poole, UK

09.30 Robotic multivisceral resection
Paris Tekkis, London, UK

10.00 SATELLITE SYMPOSIUM Karl Storz

11.30 Neoadjuvant chemotherapy for advanced colon cancer: clinical and pathological results
Dion Morton, Birmingham, UK

12.30 Colorectal surgery and hyperthermic intraoperative chemotherapy for intestinal and oveal cancers: lessons learned from 2 decades of clinical trials
Vic Verwaal, Aarhus, DK

14.30 Mechanical bowel obstruction: rush to the OR or stent and dine
Neil Mortensen, Oxford, UK

15.00 Controversies in IBD surgery
André d’Hoore, Leuven, BE

16.00 How to deal with IBD and dysplasia
Janindra Wanasuriarne, London, UK

16.30 Perianal Crohn – avoiding delay and best surgical practice
Justin Davies, Cambridge, UK

17.00 Perianal Crohn – stem cell therapy and current medical approach
Gerhard Rogler, Zürich, CH

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**Wednesday, 4 Dec. 2019**

09.00 Is anastomotic leak an infectious disease
Ronan O’Connell, Dublin, IE

09.30 Is it time to invest in robotic surgery?
Antonino Spinelli, Milan, IT

10.00 SATELLITE SYMPOSIUM Intuitive

11.30 New developments in robotic systems
Dion Morton, Birmingham, UK

12.30 Posterior component separation for abdominal wall reconstruction: evolution from open to minimal invasive using the robotic platform
Filip Muyzers, Gent, BE

14.00 Colorectal 4.0 – the networked surgeon
Richard Brady, Newcastle upon Tyne, UK

14.30 SATELLITE SYMPOSIUM Olympus

15.30 The elderly colorectal patient – functional outcomes and patient reported outcomes
Isacco Montroni, Faenza, IT

16.30 The microbiome and colorectal cancer
Philip Quirke, Leeds, UK

17.00 Surgical management of rectal endometriosis
Eric Ruiller, Bordeaux, FR

17.30 EAES Presidential Lecture 3D printing for the general surgeon
Andrea Pietrabissa, Pavia, IT

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**Thursday, 5 Dec. 2019**

09.00 Management of locoregionally advanced colon cancer
Torbjørn Holm, Stockholm, SE

09.30 ROUNDTABLE
Herand Abdarian, Chicago, US
Bill Heald, Basingstoke, UK

11.30 The mesentery in colorectal diseases
Calvin Coffey, Lumineche, IE

12.00 Technical pearls and typical mistakes in minimal invasive colectomy
Antonio Lacy, Barcelona, ES

12.30 Choosing the right anastomotic technique in colorectal surgery
Roberto Persiani, Rom, IT

13.00 Precision surgery: past, present and future
Brendan Moran, Basingstoke, UK

13.30 Poster award
Michel Adamin, Winterthur, CH

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