Original research

T1 colorectal cancer: Poor histological grading is predictive of lymph-node metastases

Damiano Caputo a, *, Marco Caricato a, Vincenzo La Vaccara a, Chiara Taffon b, Gabriella Teresa Capolupo a, Roberto Coppola a

a Department of General Surgery, University Campus Bio-Medico di Roma, Via Alvaro del Portillo, 200, 00128 Rome, Italy
b Department of Pathology, University Campus Bio-Medico di Roma, Via Alvaro del Portillo, 200, 00128 Rome, Italy

A R T I C L E   I N F O

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A B S T R A C T

Introduction: After complete local excision of pT1 colorectal cancers, prediction of the absence of lymph-node involvement represents an interesting perspective in order to avoid unnecessary additional radical surgery, reducing morbidity, mortality and costs of care.

We aimed to identify independent risk factors predictive of nodal involvement in pT1 colorectal cancer patients.

Methods: Data regarding depth of submucosal invasion, histological grading, tumour budding and lymphovascular invasion in a consecutive series of 48 pT1 surgically resected colorectal cancers have been retrospectively collected and related to the nodal status.

Results: A 12.5% rate of nodal involvement has been found. The poor differentiation was found as the only independent predictor of nodal metastases in pT1 colorectal cancer (p = 0.01).

Conclusions: Poor differentiation was the only independent significant predictor of nodal involvement in pT1 colorectal tumours. Our and literature’s data confirm that risk factors must be prospectively collected and reported; further genetic and epigenetic predictive factors have to be investigated in order to carefully evaluate the needing of major surgery for pT1 colorectal cancer.

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1. Introduction

A T1 colorectal cancer is defined as an invasive carcinoma that involves the submucosa layer but do not spread beyond it (TNM AJCC Cancer Staging Manual 7th edition, 2009).

Despite recent advances and improvement in surgical techniques, mortality and morbidity rates up to 4.5% and 40.4% respectively have been reported in colorectal cancer surgery.

In node negative pT1 patients, local excision could achieve the cure with lower morbidity, mortality and costs and improved quality of life when compared to radical surgery.

Almost 15% of T1 tumours are reported to have nodal metastases which are strictly related to disease progression and adverse outcome; it means that 85% of such patients could be definitively treated with local excision (endoscopic or surgical resection) avoiding major complications and additional costs.

On this basis, several pathological features have been investigated and reported as potential indicators of adverse outcomes after conservative management such as minor excision. The most widely considered parameters are both qualitative (tumour grade, vascular and lymphatic invasion and tumour budding) and quantitative (e.g. Haggitt’s and Kikuchi’s system). Several experiences with different conclusions on this topic have been reported in literature.

A careful prediction of the risk of nodal involvement is crucial in order to select patients who need more aggressive treatment. On this basis several histopathological features that may correlate with nodal status have been identified.

In the present study we describe our experience with identification and assessment of pathological risk factors for lymph-node metastases in pT1 colorectal cancer.

2. Materials and methods

All patients admitted to the Department of Surgery of the University Campus Bio-Medico di Roma who underwent colectomy and lymphadenectomy for pT1 colorectal carcinoma from 2001 up to date have been considered eligible in the present study.

Diagnosis of pT1 tumour was obtained after endoscopic polypectomy or radical surgery. Pathological report of pT1 endoscopic...
completely excised tumour has always been considered indication to major surgery.

Preoperative chemoradiation was performed only in locally advanced rectal tumours and was never used with sphincter-saving finality in pT1 rectal cancers. After neo-adjuvant chemoradiation, ypT1 lesions were never observed.

Data regarding depth of submucosal invasion, grade of differentiation, lymphovascular invasion and tumour budding were collected according to the European recommendations by a single pathologist.3

The depth of submucosal invasion was defined according to Haggitt’s criteria for polypoid tumours (19 cases), and to Kikuchi’s system for flat lesions (29 cases).

Grade of differentiation was classified according to the WHO classification in well (G1), moderately (G2) and poorly differentiated (G3) adenocarcinoma.4

Lymphovascular invasion i.e. tumour cells within small luminal structures lined by endothelial cells has been reported as absent or present.

Tumour budding i.e. the presence of small clusters or single infiltrating tumour cells at the front of tumour has been assessed as absent, low grade (<9 clusters or single cells) or high grade (>9 clusters or single cells).3

For patients admitted from 2001 to 2011 a re-examination of pathological slides was needed aiming to achieve missing data. Pathological slides of patients from 2011 up to date are routinely evaluated by the same dedicated pathologist and reported according to the above mentioned recommendations.

2.1. Statistical analysis

All collected data have been analysed in relation to the nodal status detected at the surgical specimen’s pathological evaluation. Differences have been analysed using Pearson’s chi-square test and two-sided Fisher’s exact test. P value <0.05 has been considered statistically significant; univariate analysis has been performed in order to identify any risk factor for lymph-node metastases by logistic regression analysis.

The Statistical Package for the Social Sciences 17.0 for Windows (SPSS Inc.) program has been used.

3. Results

A total of 48 patients with a median age of 71 years (range 40–87 years) were suitable for the analysis. There were 23 males (47.9%) (median age 73 years, range 40–79 years) and 25 females (52.1%) (median age 70 years, range 40–87 years). In the all series the median number of lymph-nodes harvested was 19 (range 5–55). There were 6 pN1 (12.5%). The median number of positive node retrieved was 1 (range 1–2). Two patients were lost at follow-up and 2 died because of other diseases. Among the remaining 44 patients all were free from disease after a median follow up of 46 months (range 1–115). Characteristics of the series are shown in Table 1.

The relationship between the nodal status with depth of submucosal invasion, tumour grading, tumour budding, and lymphovascular invasion showed that histological differentiation was the only predictive factor on nodal involvement (p = 0.01) (Table 2).

On logistic regression analysis the tumour grading remained a statistically significant predictor (Odds Ratio [OR] = 12.00; 95% CI, 1.786–80.612; p = 0.01).

4. Discussion

In our experience we detected absence of nodal involvement in presence of well differentiated tumours, as well as in Haggitt 1–2 or Sm1–2 and absent and low tumour budding. This seems to identify a low risk subset of patients, but statistical analysis failed to show a negative predictive value for these features. In opposite, the only independent factor predictive of lymph-nodes metastases is the poor differentiation, while the additional factors analysed failed to show a significant correlation with nodal involvement.

Many studies can be found on this topic, with non univocal results.

One of the first paper that systematically analysed the risk factors for lymphatic involvement in pT1 colorectal cancers was written by Ueno in 2004.2 In his paper 292 pT1 colorectal tumours were retrospectively analysed; poor differentiation, lymphovascular invasion and tumour budding were the 3 independent factors associated with lymph-node metastases. The absence of all these unfavourable factors was related to a 1% nodal involvement rate. In presence of 1 or 2–3 of these features, nodal involvement rates of 21% and 36% respectively have been observed. According to Ueno,2

<table>
<thead>
<tr>
<th>Nodal status</th>
<th>N0/N1</th>
<th>N0/N1</th>
<th>N0/N1</th>
<th>N0/N1</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth of invasion (Polypoid tumours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Haggitt 1</td>
<td>3 (100)/0</td>
<td></td>
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<tr>
<td>Haggitt 2</td>
<td>3 (100)/0</td>
<td></td>
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<tr>
<td>Haggitt 3</td>
<td>7 (77.8)/2 (22.2)</td>
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<tr>
<td>Haggitt 4</td>
<td>3 (75)/1 (25)</td>
<td></td>
<td></td>
<td></td>
<td>0.64*</td>
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<tr>
<td>Depth of invasion (Flat tumours)</td>
<td></td>
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<tr>
<td>Sm1</td>
<td>7 (100)/0</td>
<td></td>
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<tr>
<td>Sm2</td>
<td>4 (100)/0</td>
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<tr>
<td>Sm3</td>
<td>15 (83.3)/3 (16.7)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Grading</td>
<td>Well-moderate</td>
<td>Poor</td>
<td></td>
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<tr>
<td>Absent/low grade</td>
<td>36 (94.7)/2 (5.3)</td>
<td>6 (60)/4 (40)</td>
<td></td>
<td></td>
<td>0.36*</td>
</tr>
<tr>
<td>Budding</td>
<td>Absent</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>17/0</td>
<td></td>
<td></td>
<td></td>
<td>0.01*</td>
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<tr>
<td>Lymphovascular invasion</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>35 (87.5)/5 (12.5)</td>
<td></td>
<td></td>
<td></td>
<td>0.07*</td>
</tr>
<tr>
<td>Present</td>
<td>7 (87.5)/1 (12.5)</td>
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</tbody>
</table>

* Pearson’s chi-squared test.

b Fisher’s exact test.
we grouped moderately differentiated tumours with well differenti-
ated ones.

Tumour grading has been reported as predictive of nodal
involvement for pT1 together with other features such as tumour
budding, lymphovascular invasion and depth of submucosal inva-
sion by several Authors.1,2

A systematic review published in 2008 classified pT1 colorectal
cancer as having a high or low risk of recurrence.3 A low risk cancer
was defined as a completely excised, Haggitt level 1–3 or Kikuchi
Sm1, well differentiated carcinoma in absence of lymphatic or
vascular invasion. A high-risk cancer was defined as a poorly
differentiated, Sm2–3 or with lymphatic or vascular invasion car-
cinoma; extension of the tumour to resection margin always im-
plies high risk. Thus, further factors have been identified as related
to a poorer outcome such as tumour budding and perineural
invasion.

Chang,9 Huh6 and Salinas7 retrospectively reviewed series of
both pT1 and pT2 patients, respectively with 943, 224 and 82
surgically resected patients, identifying as risk factors the first
lymphovascular invasion and poor differentiation, the second
lymphovascular and perineural invasion and the third Sm3 level
and beyond as risk factors for nodal involvement. The latter con-
cludes in low risk tumour population that cut-off between Sm 1–2 and
Sm3 level is more likely to discriminate lymphatic spread than
between T1 and T2.

Tateishi10 retrospectively analysed 322 pT1 colorectal cancer
patients; risk of lymph-node involvement was significantly related
to the presence of at least one of the following factors: lymphatic
invasion, poor tumour differentiation, tumour budding or complete
disruption of the muscularis mucosa due to the tumour invasion.

More recently, Benizri11 on a series of 64 pT1 colorectal tumours
showed how the risk of unfavourable oncological outcome (such as
lymph node metastases or persistence of residual tumour) was
associated to the presence of at least 2 of these factors: no free
margin, lymphovascular invasion, poorly differentiated grade,
Sm2–3 involvement (submucosal invasion greater than 300 μm
from the muscularis mucosae); thus, lymphovascular invasion was
a predictive factor of lymph-node metastases and residual carci-
noma, but not Sm2–3 invasion. On the basis of these findings, the
Author proposed an invasive approach to endoscopic removed pT1
in presence of 2 or more of the above mentioned criteria; however,
for patients aged 65 years or younger, with a good performance
status, the surgical resection was legitimate even in presence of a
single criterion.

In a series of 55 pT1 tumours, Kye12 analysed the relation be-
tween the presence of nodal metastases and the following features:
tumour size, depth of submucosal invasion, histologic grade, lymph-
vascular invasion, tumour budding, and microacinar structure.
The tumour budding resulted the only predictive independent
factor for lymph-node metastases.

Similar conclusions have been reported by the Japanese
Kobayashi13 on 68 patients who underwent additional colectomy
after endoscopic mucosal resection for pT1 colorectal cancer. In this
experience, the only independent unfavourable prognostic factor
for nodal metastases is the moderate or poor differentiation;
however, in his opinion, only well differentiated pT1 tumours
without lymphovascular invasion should not be submitted to
additional radical surgery after minor excision. He reported a 3.8%
rate of lymph-nodes metastases in G1 pT1 and 25% in others, but
his series differs from ours since most of the patients are identified
as G1 (76.5%) and others are analysed together (23.5%); while in our
series, rates of differentiation are 16.7% for G1, 62.5% for G2 and
20.8% for G3.

On the basis of this brief analysis of literature and of our results
we could agree with others Authors that up to date it is not possible
to safely predict risk of nodal metastases in locally endoscopic or
surgical completely resected pT1 tumours. Poor differentiation,
lymphovascular invasion and tumour budding should be consid-
ered risky conditions. Pathologists may be encouraged to include
in their clinical reports data about all of the above-discussed features
according to the European guidelines.

According to most Authors, a positive margin after local excision
should always be considered sufficient to proceed with more
aggressive treatment.

In all the cases of negative margins, risk factors for lymph-node
metastases should be always carefully evaluated. Age, general
health and socio-economic status should be always considered too.
For this reason, the decision making process should be multidis-
ciplinary: pathologist, surgeon, medical oncologist and anaes-
thesiologist may be involved.

In presence of well differentiated, Haggitt 1-Sm1 pT1 which
does not present high tumour budding neither lymphovascular
invasion, a wait and see policy could be considered taking in
account:

- a) patients comorbidities;
- b) level of compliance to close follow-up regimens;
- c) patients age;
- d) risk of surgery-related complications.

Our study has some limitations such as its retrospective design
and the small size; however, our series is not selected since all the
pT1 patients in the time span have been analysed.

5. Conclusion

It should be very useful to identify a subset of patients with very
low or absent risk of nodal metastases, but our results, as well as
most of the reported studies, do not allow this conclusion. This is
related not only to the low number of cases, but also to the occa-
sional report of nodal metastases even in low risk patients. This is
why further prospective studies are needed on this topic in order
to identify subset of patients which can benefit of a wait and see policy
with close follow-up regimens, probably studying genetic and
epigenetic factors more strictly related to tumour spread.

Ethical approval

Retrospective analysis.

Funding

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Author contribution

Study design: Damiano Caputo.
Data collections: Damiano Caputo, Chiara Taffon and Gabriella
Teresa Capolupo.
Data analysis: Vincenzo La Vaccara.
Writing: Damiano Caputo and Marco Caricato.
Critical Revision: Roberto Coppola.

Conflicts of interest

None.

References

colorectal surgery for colon cancer: impact of length of stay relative to other


