Predicting Lymph Node Metastases in pT1 Rectal Cancer

S. L. Bosch and I. D. Nagtegaal

Abstract

With the widespread introduction of population screening for colorectal cancer in Europe, the number of early rectal cancers is expected to increase. In the past, approximately 25 % of rectal cancers presented with early disease, defined as stage I disease. First, results from population screening in the UK demonstrate an increase to approximately 50 % stage I for screen-detected carcinomas. In the absence of lymph node metastases, local excision of the tumor might be an attractive option, with considerably less morbidity due to surgery and a lower mortality. This option demonstrates the need for a reliable method of lymph node metastasis prediction in early rectal cancer. The overall risk of lymph node metastasis in pT1 tumors is still considerable, 11.4 %. In order to avoid both under—and overtreatment, we need adequate risk factors.

1 Increase in Early Rectal Cancer

Following Council Recommendations of the European Union, many countries have been installing national bowel cancer screening programs. Different screening modalities have been applied, aimed at both a high participation rate and high detection rates. The use of (immunochemical) fecal occult blood testing and (partial) colonoscopy will both result in increased numbers of colorectal

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carcinomas (CRC). However, as already observed in the early screening trials (Hardcastle et al. 1996), screen-detected CRC are detected at an early stage. Recent data from the current UK program show an increase from 14.7 % stage I tumors in the unscreened population (Steele et al. 2012) to 49.9 % in the screen-detected tumors. Patients with these early tumors have an excellent prognosis. Local excision is an attractive option, especially in the pT1 tumors, since it is associated with less morbidity and mortality (Wu et al. 2011). From the oncological point of view, this can be a safe procedure, provided that there are no lymph node metastases (LNM). Local recurrence might be an issue, when resection margins are not free, but this is outside the scope of the current paper.

2 Risk on Lymph Node Metastasis

LNM have since long been recognized as an important risk factor in CRC. The presence of LNM is associated with a poor prognosis, and, as a consequence, adjuvant therapy is indicated after surgery. In tumor staging, the number of involved lymph nodes is important, with a pN1 stage for 1–3 positive nodes, and a pN2 stage for 4 or more LNM. More recent, the number of lymph nodes removed and examined has received considerable attention as an important issue in lymph node staging (Shia et al. 2012). Not only is the number of examined lymph nodes considered an independent prognostic factor (Swanson et al. 2003), but it is also thought that a larger number of lymph nodes is associated with an increased likelihood of detecting LNM. However, there is some debate on the latter, since in general LNM are larger and easier to detect than negative lymph nodes. Whether increasing numbers of lymph nodes also lead to increased numbers of nodes with micrometastases remain to be investigated. The presence of micrometastases is associated with disease recurrence in stage I and II CRC (Sloothaak et al. 2014), and these are hard to detect on preoperative imaging.

In general, the risk on LNM increases with increasing tumor invasion depth and increasing tumor size (Mekenkamp et al. 2009). In pT1 tumors, the overall risk on LNM is 11.4 %, as has been analyzed in a systemic review of 3,621 patients (Bosch et al. 2013). However, there are histological factors that allow for a more individualized risk estimation.

3 What Can We Measure?

As mentioned above, the risk on LNM increases with increasing size and invasion depth of the tumor. Within the pT1 group, this still holds true. Submucosal invasion depth can be subclassified applying a qualitative or a quantitative definition on sessile carcinomas. The qualitative or semiquantitative definition of Kudo (1993) uses the relative submucosal levels: sm1 (uppermost 1/3), sm2 (middle 1/3), and sm3 (deepest 1/3 of the submucosa) (Fig. 1). Indeed, an increasing frequency of lymph nodes are observed: 3.4 % (sm1), 8.5 % (sm2), 22.6 % (sm3) (Bosch et al.

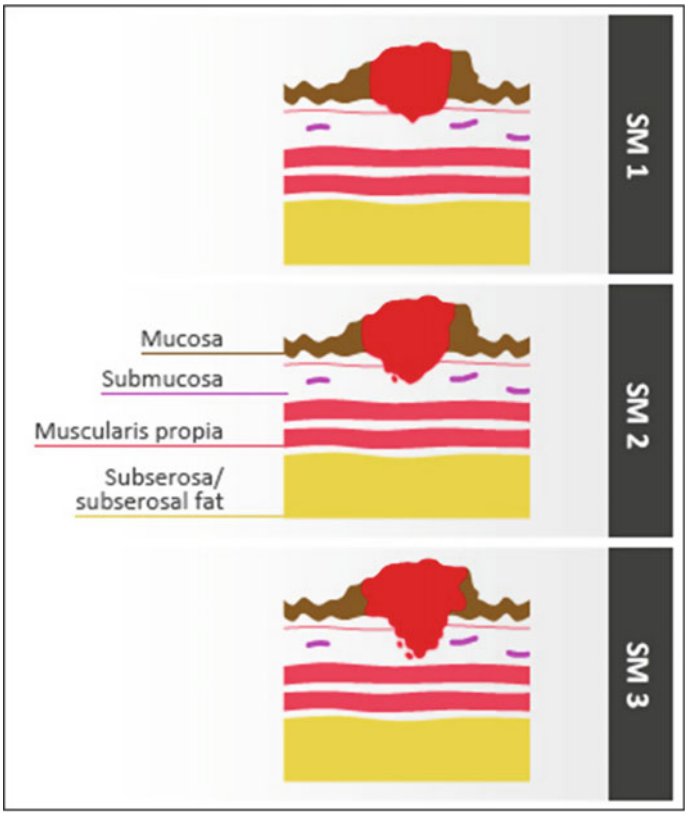

Fig. 1 Kudo classification

2013). However, this method is hard to apply when the muscularis propria is not present in the resection. Alternatively, exact measurements can be used to predict LNM: cut-off levels of 1 and 2 mm have been suggested. Risk on LNM is extremely low in case of an invasion depth less than 1 mm (1.5 %), however, this is a small group of patients (Bosch et al. 2013). Invasion over 1 mm is associated with 12.3 % LNM, and invasion depth over 2 mm is associated with 13.3 % LNM (Bosch et al. 2013). It should be noted that these percentages are only slightly increased compared to the average risk for a pT1 tumor, and as such, these findings in itself do not warrant a radical resection.

For cancers developing in polyps, the measurements of invasion depth are more difficult. A semiquantitative measurement has been introduced by Haggitt et al. (1985) (Fig. 2). A limited number of studies apply this classification, and the increased risk on LNM seems only present in level 4 CRC.

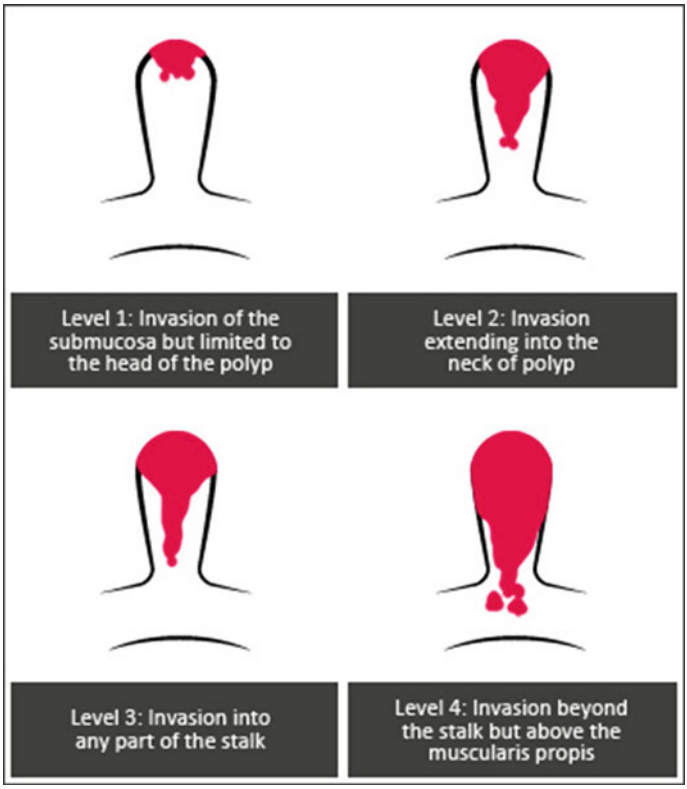

Fig. 2 Haggitt classification

An alternative for tumor size is submucosal width, which is investigated in three studies with a total number of 620 patients (Bosch et al. 2013). Larger tumors with a submucosal width of over 5 mm showed LNM in 17 % compared to 5.6 % in the smaller tumors.

4 Monitoring Tumor Behavior

Risk on LNM is also dependent on tumor biology. Molecular biomarkers are currently being investigated, but none are ready for diagnostic routine. However, growth pattern and interactions with the tumor microenvironment have been investigated in more detail and add relevant information for the risk estimation. Many studies have examined the role of differentiation grade in early adenocarcinomas. Grading is based on the percentage of gland formation in the tumor (World Health Organization. 2010), with a well-differentiated tumor entirely consisting of relatively well-defined glands, and poorly differentiated tumors that consist of areas with a solid growth pattern. For clinical use, the terms low grade (i.e., well and moderately differentiated)

and high grade are preferred. Other tumor types, such as mucinous carcinoma en signet ring cell carcinoma, are in most studies grouped with high-grade tumors. The presence of high grade is associated with an increased risk of LNM, 24.5 versus 8.9 % in low-grade lesions (Bosch et al. 2013).

Separately, the differentiation at the invasive front of the tumor is considered to be important. Sometimes poorly differentiated clusters are observed here (Ueno et al. 2013), that are strongly correlated with the process of budding. Not all studies distinguish these two factors, there might be significant overlap. Budding is sprouting of the tumor, and small groups or single cells infiltrate the microenvironment. While definitions of budding differ per study, tumor buds are in general defined as less single cells or clusters of less than five cells. Poorly differentiated clusters are defined as five cells or more, clustered without evidence of gland formation (Ueno et al. 2013). In the systemic review, the impact of budding on LNM was more pronounced than the effect of the poorly-differentiated clusters (5 vs. 21.3 % and 10.2 vs. 19.2 %, respectively) (Bosch et al. 2013).

In the development of LNM, invasion of the lymphatics play a key role, which is reflected by the high percentage of LNM in the presence of lymphatic invasion (26.7 %) (Bosch et al. 2013). Not all studies report lymphatic invasion as a separate entity, but use lymphovascular invasion as an alternative, grouping lymphatic and vascular invasion. While vascular invasion in itself is associated with a poor prognosis, it is not directly related to the development of LNM and thus not such an adequate risk factor.

5 Overview of Relevant Factors

In a recent meta-analysis, we have studied most of the histological factors that are associated with LNM in pT1 tumors (Bosch et al. 2013). Figure 3 gives an overview of all relevant factors and their impact on the prediction of LNM. In order to establish the value of all factors, sensitivity, specificity, positive, and negative predictive value should be taken into account. Sensitivity is especially high for submucosal invasion depth (1 mm), with 96.7, however, this is accompanied by a low specificity, that causes a high false-positive rate and many unnecessary radical resections. Specificity is high for poor differentiation, which is associated with low sensitivity. Positive predictive values are relatively low for all factors, but negative predictive values are 90 % or above. This illustrates the need for a comprehensive approach, in more factors should be combined for optimal decision-making.

6 Future Considerations

With increasing numbers of patients potentially eligible for local excision of rectal carcinoma, there is an obvious need for adequate risk estimation. Existing studies have identified histological risk factors that can be applied in daily practice, but need confirmation in large populations. We need to focus on combinations of

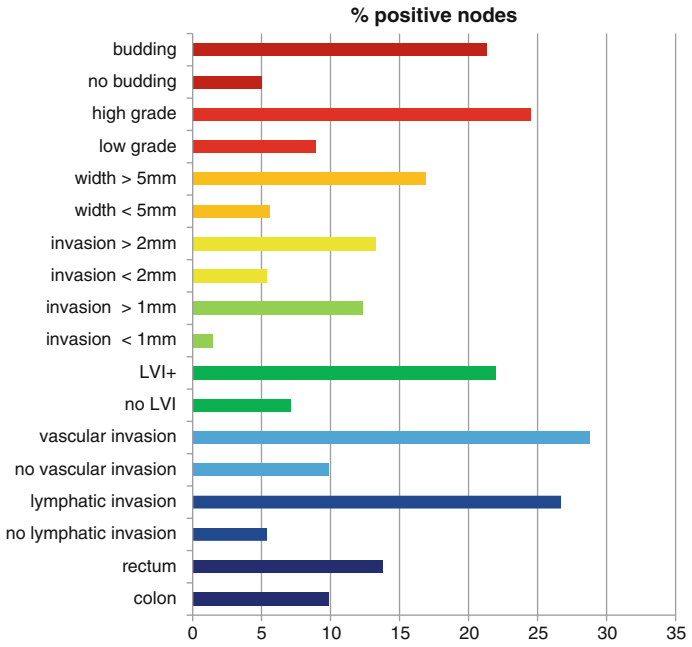

Fig. 3 Histological risk factors for LNM. *Source* Based on the systematic review from Bosch et al. LVI: lymphovascular invasion

factors to stratify patients according to LNM risk. Since the large studies in pT1 tumors originate from Asian countries, with a more extensive pathological workup, we need to validate the risk factors in Western cohorts. In addition, we need validation within screen-detected carcinomas. In breast cancer, it has been suggested that screen-detected carcinomas have a biological distinct background (Dawson et al. 2009), these tumors supposedly are less aggressive. The standardized data collection that is part of the screening programs will offer insights on this issue within a couple of years.

Another issue that needs to be addressed is the application of neoadjuvant therapy. In rectal cancer, this therapeutic strategy has been applied for years, in various combinations of radiotherapy and chemotherapy. In a large number of cases, significant downstaging as a result of treatment made less extensive surgery a possibility. Tumors that decrease in size to ypT0 or ypT1 could potentially be treated with local excisions. However, risk on LNM in these populations might be very different. Even with a complete response of the primary tumor (ypT0), still 7 % of cases present with LNM (Nagtegaal and Marijnen 2008). In these cases, there are no histological risk factors that can be examined. However, risk factors in ypT1 and ypT2 tumors need to be identified, because adequate risk stratification based on histological characteristics may prevent both over and undertreatment of these patients.

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