Sentinel Lymph Node Biopsy during Right Hemicolecction
- A Systematic Review

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Abstract

Right hemicolecction and Sentinel Lymph Node Biopsy (SLNB) is an alternative to standard right hemicolecction with D2 lymphadenectomy. Right hemicolecction and SLNB may potentially increase lymph node harvest; however current techniques may offer a low sensitivity.

The aim of this systematic review was to review the literature in relation to right hemicolecction and SLNB and compare it’s outcomes to those of standard right hemicolecction to determine if right hemicolecction and SLNB could lead to improved patient outcomes in right colonic cancer.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed in undertaking this study [14].

MEDLINE was searched to identify all studies describing right hemicolecction with SLNB from 2008-2018. Statistical analysis was performed using the ‘Meta’ and ‘Metafor’ packages in R statistical software [18,19].

Results: Nine studies with a total of 5096 patients were included in this review of right hemicolecction with SLNB. SLNB is associated with high lymph node harvests (mean 28.8); however concerns exist regarding its sensitivity in patients with elevated body mass indexes.

Conclusion: Right hemicolecction with SLNB may upstage and potentially improve prognosis in colorectal cancer, however this procedure may increase patient morbidity and mortality. Further research is necessary to definitively evaluate this technique.

Introduction

Patients with early stage colorectal cancer have five-year survival rates of between 82 and 93%; this decreases to 59% in the presence of lymph node metastases [1].

Traditionally a segmental colectomy with D2 lymphadenectomy was performed based on the oncological principle that local control of disease dictated survival. Lymphadenectomy was performed for pathological staging purposes and prognostication, rather than actual survival benefits [2].

Of the patients with colorectal cancer without lymph node metastases who are treated with potentially curative surgery, 20% to 30% will die of this disease within five years; this may be explained in part by under-staging of the disease because of an insufficient lymph node yield.

Decisions made by the colorectal team regarding adjuvant chemotherapy are largely based on nodal status. Patients with stage two colorectal cancers are treated with a segmental colectomy and D2 lymphadenectomy providing that they are fit for surgery. If histopathological analysis of the resected lymph nodes demonstrates absence of tumor, adjuvant chemotherapy is in general not required [3].

Patients with stage three colorectal cancers are treated with surgical resection of the segment of colon containing the tumor and D2 lymphadenectomy followed by adjuvant chemotherapy [3]. Adjuvant chemotherapy in patients with lymph node infiltration has decreased mortality by more than 30% [4].

Survival from colorectal cancer is improved when the lymph node harvest is increased, especially when these lymph nodes are negative [5]. Survival is also improved when a large number of lymph nodes are retrieved even if some of these nodes are infiltrated by tumor as this may upstage a patient.
from stage two to stage three cancers allowing these patients to access adjuvant chemotherapy [5].

The American Joint Committee on Cancer (AJCC) recommends analyzing at least 10-14 lymph nodes for accurate staging of disease [6]. Lower lymph node harvests may under-stage disease resulting in patients not receiving adjuvant therapy [7].

The surgical treatment of colorectal cancer now stands at a crossroads with a very different surgical strategy currently being evaluated.

**Right hemicolecotomy and SLNB**

Right hemicolecotomy and sentinel lymph node biopsy is an alternative to standard right hemicolecotomy with D2 lymphadenectomy.

The sentinel lymph node is the hypothetical first lymph node or group of lymph nodes that drain a cancer. Sentinel lymph node biopsy is highly effective in correctly predicting nodal status for both melanoma and breast cancer patients [8,9]. In contrast, the current evidence for sentinel lymph node biopsy in colon cancer is conflicting [10].

Advocates of right hemicolecotomy and sentinel lymph node biopsy claim that it is a selective sampling technique that can be used to ultra-stage regional nodes. Supporters of this technique report a high predictive value of sentinel lymph node biopsy for the nodal status. They further hypothesize a more accurate staging of colorectal cancer by detection of small tumor deposits and in addition they report an increased yield of harvested lymph nodes [10]. Proponents of the sentinel lymph node technique in colonic cancer also report a significant percentage of aberrant drainage outside the planned resection margins [10]. Thus when right hemicolecotomy is performed with sentinel lymph node biopsy, involved lymph nodes are argued to be identified and removed with the specimen. This aberrant drainage and the identification of possibly involved lymph nodes would not have occurred during standard right hemicolecotomy and D2 lymphadenectomy. Consequently the use of the sentinel lymph node biopsy technique may upstage patients with colorectal cancer, allowing access to adjuvant chemotherapy with potentially an improvement in prognosis [10].

Critics of the sentinel lymph node biopsy technique in colon cancer claim that the technique is associated with a limited colonic resection and potentially a sub-optimal resection of the colonic tumor [10]. Those who support the use of the sentinel lymph node biopsy technique in colorectal cancer argue however that the tumor status of the sentinel lymph node does not change the extent of resection because en-bloc resection of the primary colon cancer includes regional lymph nodes, and therefore a sub-optimal surgical resection does not occur during segmental colecotomy and sentinel lymph node biopsy [10].

The strongest endorsement for this technique is the that results of sentinel lymph node-based nodal ultra-staging can improve identification of candidates for adjuvant chemotherapy, a treatment that is highly effective for metastatic disease, with the potential for an improved prognosis in patients with colorectal cancer [10].

During histopathological examination of the specimen following standard right hemicolecotomy with D2 lymphadenectomy, nodes in the resected specimen are identified by visualization and palpation. Nodes <0.5 cm in diameter with potentially metastatic disease may be missed by this technique, however the sentinel lymph node can be identified with either in vivo or ex vivo mapping and hence small lymph nodes are less likely to be missed [11].

Sentinel lymph node biopsy using methylene blue performed ex vivo can accurately predict nodal status in patients with colorectal cancer, and studies have demonstrated that this technique can achieve upstaging of patients from stage one or two to stage three disease, enabling these patients to access chemotherapy with resultant improvement in prognosis that would not have occurred with standard lymph node sampling [12].

The disadvantage of sentinel lymph node biopsy in colorectal cancer is the procedure sensitivity rate, with some studies suggesting that this is as low as 54% [13]. Those who support this technique however would argue that the sentinel lymph node biopsy technique is almost as sensitive in colorectal cancer as it is for melanoma and breast cancer [13].

In light of the above, the aims of this study were to determine if right hemicolecotomy with SLNB is associated with improved outcomes compared to standard right hemicolecotomy for patients with surgically resectable right colon cancer. This study also aimed to determine if patient morbidity and mortality with right hemicolecotomy and SLNB were comparable to those associated with standard right hemicolecotomy.

**Methods**

**Inclusion and exclusion criteria**

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in undertaking this systematic review and meta-analysis (Figure 1) [14].

All published studies on right hemicolecotomy with Sentinel Lymph Node Biopsy (SLNB) were included. It was necessary to include all studies during this review as there are currently no randomized controlled trials for right hemicolecotomy with sentinel lymph node biopsy (Table 1).

Studies were included that measured any or all of the following primary and/or secondary outcomes: 30 day morbidity, 30 day mortality, anastomotic leakage, intra-operative blood loss, 5 yr overall survival, disease-free survival, local recurrence, length of surgery, post-operative ileus, duration of post-operative stay and number of lymph nodes harvested.

Definitions of the end-points were based on the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 [15].

Anastomotic leakage required a CT scan or intra-operative diagnosis. Ileus was defined as an inability to tolerate an oral diet more than 24 hrs after the operation, despite regular anti-emetics; or dilatation of the bowel on CT scan without a mechanical transition point, requiring placement of a nasogastric tube.

Systematic reviews and meta-analyses, editorial comments, reviews and responses to articles were excluded. Studies were restricted to those published in the English language (Table 1).

**Search and selection strategy**

A comprehensive literature review was performed by the author on 23rd February 2018. A search of MEDLINE via Pubmed and Medline via Ovid SP was undertaken to identify all studies describing the use of ‘sentinel lymph node biopsy and right hemicolecotomy’ in
patients with colorectal cancer.

The search terms used were: ‘colon cancer AND sentinel lymph node biopsy’ searched as both keywords and MeSH headings where available.

Search results were first screened by title and abstract, after which the full texts of potentially relevant articles were retrieved and underwent a further round of screening for inclusion. The references of included studies and relevant review articles were manually searched for additional suitable publications.

Inclusion criteria were:
- All publications evaluating patients with colorectal cancer undergoing right hemicolectomy with sentinel lymph node biopsy
- Adult patients only
- Studies in the English language only
- Studies published in full form in peer-reviewed literature

Data extraction and validity assessment

Data was extracted and quality control was performed by the author. Any discrepancies in the data were resolved by involvement of the study supervisor. Where additional data was required, the corresponding author of the relevant article was contacted by email in an attempt to obtain the necessary data.

For each included article, the following data and outcomes were extracted in a structured information sheet: author of study, study design, study centre/country, type of resection, use of Enhanced Recovery after Surgery (ERAS) protocol, primary outcome, follow-up duration, main findings from the study [16] (Table 1). In addition data was also collated on: patient demographics (age, body mass index), numbers of patients in the study, 30 day morbidity, 30 day mortality, rates of anastomotic leak, volume of intra-operative blood loss, 5 yr overall survival, disease-free survival, local recurrence, length of surgery, duration of post-operative ileus, post-operative duration of hospital stay and the number of lymph nodes harvested (Table 1).

Studies that did not meet the inclusion criteria were removed prior to the systematic review and meta-analysis. [17-20].

Data analysis

Outcome measures were calculated as pooled proportions of patients (with 95% confidence intervals) developing the outcomes of interest. The fixed effects (Mantel-Haenszel) and random effects (Der Simonian-Laird) models were used for pooling.

A fixed effect meta-analysis assumes all studies are estimating the same (fixed) treatment effect, whereas a random effects meta-analysis allows for differences in the treatment effect from study to study.

Heterogeneity was determined using the Q statistic of I2 which describes the percentage of total variation across studies attributable to heterogeneity rather than to chance [21]. An I2 value of 0% to 25% was taken to represent low heterogeneity, 26% to 50% moderate heterogeneity, and values above 50% represented high heterogeneity. Heterogeneity was assessed by examining the Forest plots for obvious outliers and by attempting appropriate subgroup analyses. In general, the fixed-effects model was used in analyses with low heterogeneity while the random-effects model was used in instances of high heterogeneity. Statistical analysis was carried out using the ‘Meta’ and ‘Metafor’ packages in R statistical software version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) [22,23].

Quality assessment of the included studies was carried out using the NHLBI Study Quality Assessment Tools for Observational Cohort and Cross - Sectional Studies and Case-Control Studies [24].

Results

Selection and quality assessment

Systematic review: right hemicolectomy with SLNB: Thirteen studies were retrieved from the initial search, however after removal of one meta-analysis [17], one response article [18], one systematic review [19], and one editorial comment [20], nine studies were left for the systematic review (Table 1 and Figure 1).

No randomized controlled trials currently exist that compare right hemicolectomy and sentinel lymph node biopsy to standard right hemicolectomy and D2 lymphadenectomy. Five of the nine studies were case control series, one study was a population-based study, one study was a case report, one was a prospective feasibility study and one study was a secondary intention analysis of two prospectively maintained databases to allow multi-centric data analysis (Table 1).

Patient ages ranged from 46-67 years and patient body mass indexes ranged from 26.6-28.4 kg/m².

A total of 5096 patients were included in the nine studies. None of the studies reported information on 30 day morbidity, 30 day mortality, rates of anastomotic leak, intra-operative blood loss, five year overall survival, disease-free survival, local recurrence, length of surgery, duration of post-operative ileus, or post-operative duration of hospital stay. Four of the nine studies recorded information on...
number of lymph nodes harvested and this ranged from 14.3-32.9 nodes (Table 1).

**Discussion**

Insufficient data was retrieved from the systematic review on right hemicolectomy with sentinel lymph node biopsy for a meta-analysis to be performed. Therefore the results of the systematic review for right hemicolectomy and sentinel lymph node biopsy will be discussed.

This systematic review has analyzed all peer-reviewed studies printed in English on this subject over a ten year period from 2008 until 2018. To date no randomized controlled trials exist that compare right hemicolectomy and sentinel lymph node biopsy to right hemicolectomy with D2 lymphadenectomy. The data presented however represents a combined number of 5096 patients and hence an accurate discussion with suggestions for the future application of this procedure can be generated from this systematic review.

None of the studies analyzed during this systematic review gave information on 30 day morbidity, 30 day mortality, rate of anastomotic leak, volume of intra-operative blood loss, five year overall survival, disease-free survival, local recurrence, length of surgery, duration of post-operative ileus, or post-operative duration of hospital stay. Four of the nine studies recorded information on the average number of lymph nodes retrieved with the sentinel lymph node biopsy technique; this was 14.3, 28.4, 26 and 32.9 (Table 1).

The lymph node harvest during right hemicolectomy and sentinel lymph node biopsy is certainly more than the ten to fourteen lymph node biopsy technique; this was 14.3, 28.4, 26 and 32.9 (Table 1). Intra-operative blood loss, 5yr overall survival, Disease free survival, Local recurrence, Length of surgery, Post-op ileus, Post-op length of stay and LN Harvest are available from the studies, some interesting discussion points have emerged.

Murawa et al. state that ‘sentinel lymph node biopsy is less sensitive for tumors with deep infiltration into the intestinal wall,’ and in addition, ‘the presence of nodal metastases, lymph node capsule and peri-nodal invasion significantly alters the accuracy of sentinel lymph node biopsy in colorectal cancer’ [25]. If this conclusion is correct this undoubtedly represents a huge disadvantage of this technique, other than for very early colorectal tumors, and will limit both the use and the confidence in this technique amongst the fraternity of colorectal surgeons. Hirche et al. performed a case control series investigating the use of Indocyanine Green (ICG) fluorescence imaging with colectomy and sentinel lymph node biopsy [26]. They concluded that indocyanine green fluorescence imaging is ‘a new and feasible method for sentinel lymph node biopsy that allows ultra-staging with improved accuracy.’ Although this method warrants consideration, one must question the validity of such claims with a study population of just twenty six patients [27]. Ankersmit et al. are also strong proponents of the sentinel lymph node technique in colorectal cancer [28]. This group utilized infra-red fluorescence and laparoscopy and claimed that with their technique it would be possible to treat early colorectal cancer with local resection using

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In addition to the sentinel lymph node technique being associated with an increased lymph node yield during right hemicolectomy, it is claimed that the procedure also leads to the detection of small tumor deposits that would otherwise not have been identified during standard right hemicolectomy with D2 lymphadenectomy [10].

In theory both the increased number of lymph nodes retrieved and the identification of additional lymph nodes due to the sentinel lymph node technique should lead to an improved survival of patients with right colonic cancer by either definitively excluding cancer in an increased number of lymph nodes or by revealing metastatic spread in lymph nodes that may not have been retrieved during right hemicolectomy with standard D2 lymphadenectomy. This could potentially upstage patients from stage two to stage three cancers and allow access to adjuvant chemotherapy with its associated survival benefit [4].

All of the reviewed studies are prospective case controlled series, a secondary intentional analysis, a case report and a prospective feasibility study therefore none of the studies present level I evidence, with no randomization of study groups and the potential presence of author bias, however despite the paucity of clinical information available from the studies, some interesting discussion points have emerged.

Murawa et al. state that ‘sentinel lymph node biopsy is less sensitive for tumors with deep infiltration into the intestinal wall,’ and in addition, ‘the presence of nodal metastases, lymph node capsule and peri-nodal invasion significantly alters the accuracy of sentinel lymph node biopsy in colorectal cancer’ [25]. If this conclusion is correct this undoubtedly represents a huge disadvantage of this technique, other than for very early colorectal tumors, and will limit both the use and the confidence in this technique amongst the fraternity of colorectal surgeons. Hirche et al. performed a case control series investigating the use of Indocyanine Green (ICG) fluorescence imaging with colectomy and sentinel lymph node biopsy [26]. They concluded that indocyanine green fluorescence imaging is ‘a new and feasible method for sentinel lymph node biopsy that allows ultra-staging with improved accuracy.’ Although this method warrants consideration, one must question the validity of such claims with a study population of just twenty six patients [27]. Ankersmit et al. are also strong proponents of the sentinel lymph node technique in colorectal cancer [28]. This group utilized infra-red fluorescence and laparoscopy and claimed that with their technique it would be possible to treat early colorectal cancer with local resection using
minimally invasive sentinel lymph node biopsy procedures [29]. This is certainly a potentially exciting prospect for the future but this was a prospective case control series with undisclosed patient numbers and hence these statements should be considered with caution until Ankensmrt et al. present these results with a higher level of evidence.

In a prospective feasibility study of one hundred patients conducted by Murawa et al. patent blue in-vivo mapping was performed during open right hemicolectomy [30]. In this study it was concluded that sentinel lymph node biopsy has an accuracy of 93.9% in detecting regional lymph node status, a sensitivity of 83.3% with a false negative rate of 16.7% [30]. Importantly this group concluded that up-staging of patients occurred in 10% of cases [30]. These are impressive results and would certainly prompt consideration of this technique by colorectal surgeons, however one wonders if these results would be reproducible during laparoscopic as well as open right hemicolectomy.

A more cautious consideration of right hemicolectomy with sentinel lymph node biopsy is given by Tan et al. who advises that the sentinel lymph node may be some distance away from the primary tumor and therefore the sentinel lymph node biopsy technique cannot be used to reduce the extent of surgical resection. Tan et al. [31] conclude that the distribution of sentinel lymph node metastases over a wide area with high false negative rates argue against the use of sentinel lymph node biopsy during right hemicolectomy and advise that radical resection should remain the treatment of choice for right colonic cancers [31]. Ninety three patients were included in this prospective case control series and this certainly gives some weight to the conclusions formed by Tan et al. [31].

Dragan et al. also undertook a prospective case control series with a population of sixty patients and concluded that sentinel lymph node biopsy could potentially upstage patients from stage one to stage two or three cancers [32]. The conclusion generated from the study by Dragan et al. that sentinel lymph node biopsy during right hemicolectomy could up-stage patients with colorectal cancer is in agreement with the conclusions generated from both the trials by Hirche et al. [27] and Murawa et al. [30].

The suggestion that the sentinel lymph node biopsy technique during right hemicolectomy can upstage cancer generated from unrelated studies in Greece, Germany and Poland is a positive endorsement of sentinel lymph node biopsy during right hemicolectomy and advise that radical resection should remain the treatment of choice for right colonic cancers [31]. Ninety three patients were included in this prospective case control series and this certainly gives some weight to the conclusions formed by Tan et al. [31].

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In the nine studies discussed in the systematic review there are clear arguments for and against the use of sentinel lymph node biopsy during right hemicolectomy. The majority of supporters of this technique claim that it can upstage patients from stage one or two to stage three cancers as a result of both the increased lymph node retrieval and also due to identification of lymph nodes that would have otherwise have been missed during standard lymphadenectomy. As a result of up-staging patients have access to adjuvant chemotherapy with its associated potential improvement in prognosis [4].

The opponents of the sentinel lymph node technique argue that the drainage of colorectal cancer does not follow the same predictable pattern as that of breast cancers and malignant melanoma, and hence this gives unacceptably high false negative rates of lymph node involvement with potential for inappropriate downstaging of cancer therefore denying patients adjuvant chemotherapy with consequently a poorer prognosis.

In a study published in the Annals of Surgery by Bembenet et al. [34] it was concluded that although sentinel lymph node biopsy could upstage colorectal cancer, caution was advised in patients with body mass indexes of ≥ 30 kg/m². It was felt that in this sub-group of patients lymph channels were more difficult to identify and as such the sensitivity of sentinel lymph node biopsy might be reduced [34]. This is a significant disadvantage of the sentinel lymph node technique and would make the technique difficult to utilize in the average United Kingdom patient with a body mass index of ≥ 30 kg/m².

It should be noted however that all of the studies discussed in this systematic review of right hemicolectomy and sentinel lymph node biopsy represent at best level three evidence. Whilst interesting conclusions and discussions can be generated a double blind randomized control trial is required to definitively evaluate the advantages and disadvantages of right hemicolectomy with sentinel lymph node biopsy.

This systematic review gives a thorough evaluation of the literature currently available comparing standard right hemicolectomy with D2 lymphadenectomy to right hemicolectomy with sentinel lymph node biopsy; however this study has several limitations.

This literature review performed for this systematic review and meta-analysis examined all peer-review studies published in the English language over the ten year period from 2008 until 2018. It is possible that earlier reports describing right hemicolectomy with SLNB are available in the literature and by reviewing the literature from 2008 onwards these have been omitted from the systematic review and meta-analysis.

A further limitation of this systematic review and meta-analysis is the language bias that has been introduced into this study. By examining all peer-reviewed literature published in the English language only, potentially important studies may have been omitted from this systematic review, in particular it is highly likely that Asian studies have been omitted due to this language bias given that many of the major studies examining sentinel lymph node biopsy with right hemicolectomy have been conducted in China, Japan and South Korea.

A further major criticism of this study is the lack of randomized
controlled trials reviewed, however given the search terms used and the language and time restrictions applied, the systematic review was only able to generate case control series, case reports, observational studies, secondary intention analysis and prospective feasibility studies. Given the lack of high quality studies included in this systematic review, the evidence generated from this study is level 3A or at best level 2B.

A final major limitation of this systematic review is that the evidence generated was insufficient to perform a meta-analysis to allow definitive discussion to be generated on the pros and cons of this technique; therefore the analysis of the right hemicolecotomy with sentinel lymph node biopsy is a systematic review only.

The alternative nodal harvesting technique during right hemicolecotomy of sentinel lymph node biopsy has potentially many advantages but certainly there are obvious disadvantages and clear risks associated with this procedure. This is especially the case in the United Kingdom patient cohort. To thoroughly and appropriately evaluate this technique, it is would be essential to analyze the results of a double blind randomized control trial comparing this technique to standard right hemicolecotomy and D2 lymphadenectomy. To date there is no plans to perform a randomized controlled trial to thoroughly evaluate the advantages and disadvantages of right hemicolecotomy with sentinel lymph node biopsy; however this would provide useful information. It is doubtful that this technique will become routine practice without such high level evidence.

In summary the systematic review on right hemicolecotomy with sentinel lymph node biopsy gives quite conflicting conclusions. Certainly this technique might increase numbers of lymph nodes harvested with potential upstaging of patients allowing them to access adjuvant chemotherapy with potentially increased survival.

Some studies suggest however, that right hemicolecotomy with sentinel lymph node biopsy is poorly sensitive for tumors that have infiltrated deeply into the intestinal wall. It is also argued that this technique is unreliable because lymph node drainage from the colon does not follow the predictable pattern demonstrated in breast and malignant melanomas. Of concern also is the suggestion that this technique is less sensitive and more technically challenging in patients who are overweight, and hence the results observed in the studies analyzed in this systematic review may not be reproducible in the United Kingdom patient cohort.

Conclusion

Right hemicolecotomy with sentinel lymph node biopsy is an interesting technique that can increase lymph node yield and potentially up-stage regional lymph nodes allowing patients to access chemotherapy with an improvement in prognosis. Currently the sensitivity of this technique is not adequate for it to be safely utilized during right hemicolecotomy for colorectal cancer but with continued research and development, the sensitivity of this technique may increase, and it could then be safely utilized during localized resectional techniques to avoid the need for major surgery.

References


23. Study Quality Assessment Tools.


