The Examination of Lymph Nodes Following Surgery for Colorectal Cancer

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A thesis presented for the degree of Master of Philosophy

School of Medicine

Cardiff University

September 2011

DECLARATION

This work has not previously been accepted in substance for any degree and is not concurrently submitted in candidature for any degree.

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STATEMENT 1

This thesis is being submitted in partial fulfillment of the requirements for the degree of Master of Philosophy

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Science is facts; just as houses are made of stone, so is science made of facts; but a pile of stones is not a house, and a collection of facts is not necessarily science.

Jules Henri Poincaré (1854-1912) French mathematician

Dedication

This thesis is dedicated to the people who have sacrificed most to allow it to be completed, namely my wife Amanda and daughters Nia, Mali and Cadi. Without their support I have no doubt that it would not have come to fruition.

Acknowledgments

I am indebted to my supervisors Professor Geraint Williams and Mr Jared Torkington for their support, patience and advice that have enabled completion of this thesis.

I am extremely grateful to Mr Sharad Karandikar for his support and guidance throughout my post-graduate training and for allowing me to make his practice the subject of study in one chapter of this thesis.

There are several people that I would like to thank whose support has allowed the writing of this thesis:

- The cancer services staff, surgical staff and Lisa Jones at the Princess of Wales Hospital
- The surgeons and pathologists whose practice has been studied within this thesis
- Linda Roberts, CANISC co-ordinator for her help with data collection from the Welsh Bowel Cancer Audit
- Rebecca Thomas, WICSU statistician for obtaining survival data that has been used in this thesis

I would like to reserve particular appreciation for Mr Jeffrey Stamatakis who agreed to supervise this thesis in his retirement. I will always be indebted to him for the advice and support afforded, both with the writing of this thesis and also in so many other aspects of my professional development.

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Introduction and Literature review

Chapter 1 – Surgeon and Pathologist as variables on lymph node harvest

Chapter 2 – Impact of National audit against national guidelines on lymph node retrieval following colorectal cancer resection

Chapter 3 – Impact of nodal harvest on survival following colorectal cancer resection in Wales

Thesis Summary

Background: The number of lymph nodes (LN) harvested following colorectal cancer (CRC) resection is important for accurate LN stage discrimination and has been considered as a quality marker in the surgical treatment of CRC. Stage discrimination is critical to ensure that patients receive the optimal treatment for their disease stage and to provide prognostic information for the patient.

Aims: To identify factors that independently predicted LN harvest (LNH), study the impact of national guidelines and audit had on LNH at national level and to examine the impact that LNH has on survival of node negative and node positive CRC.

Methods: Data on patients having CRC resection at unit and national level were studied, and multivariate statistical modelling used to determine independent predictors of harvest and survival.

Results:

- The reporting pathologist is an independent variable for LNH
- The operating surgeon did not influence LNH
- Inter unit variability in LNH exists
- National audit against national standards improved nodal yield at a national level
- Increasing LNH independently predicted survival in Dukes' stage B CRC, up to a level of 15 nodes per patient.
- Lymph node ratio (LNR) independently predicted survival in Dukes' C CRC and may be a more sensitive prognostic indicator than current lymph node staging systems.

Conclusions: The principal conclusions of this thesis were that LNH is an appropriate quality indicator of combined pathological and surgical activity, but not surgery in isolation. National audit against national guidelines has improved LNH in Wales. Survival differences in node negative CRC up to a level of fifteen nodes suggests that the current national guidelines of twelve nodes per patient should be increased. LNR was found to predict survival in CRC patients suggesting it might be appropriate to include LNR in future staging systems for CRC.

Recommendations arising from the findings of this thesis

- The use of lymph node harvest as a marker of quality in colorectal cancer treatment is appropriate for combined surgeon and pathologist performance, but not surgical performance in isolation.
- In addition to participation in national audits, multi-disciplinary teams treating colorectal cancer should perform clinician identifiable intra-unit risk adjusted audit of the lymph node harvests of its surgeons and pathologists.
- The current Association of Coloproctology of Great Britain and Ireland model for risk adjusting lymph node harvest is calibrated too low and should be revised in line with contemporary data.
- The current twelve-node national harvest guidance for lymph node retrieval following colorectal cancer should be revised to a higher level and take into account differences in harvest according to tumour site.
- National audit against recommended national performance guidelines can be expected to improve adherence with the prescribed guidelines.
- In node negative colorectal cancer at least fifteen nodes should routinely be evaluated, to maximise confidence in staging
- Patients assigned a node negative status following examination of less than twelve nodes should be considered for adjuvant chemotherapy.
- Lymph node ratio should be incorporated into staging systems for colorectal cancer and patients with high lymph node ratio levels may be targeted for a more aggressive chemotherapy policy.

Ethical Approval

At the outset of this thesis the local research ethics committee for Bridgend, Neath Port Talbot and Swansea were contacted for advice about the need for ethical approval to carry out the presented research. The Chairmen and Vice-Chairman of this committee considered the thesis proposal at that time and advised, “that the project is not one that is required to be ethically reviewed under the terms of the Governance Arrangements for Research Ethics Committees in the United Kingdom”.

0.1 Introduction and Literature Review

Colorectal cancer (CRC) is the third most common cancer in the United Kingdom with over 37,000 new cases registered annually. During the last decade its incidence has remained relatively static but there has been a 16% improvement in age-standardised mortality. Even with this improvement there were over 16, 000 deaths from colorectal cancer in the United Kingdom in 2007[1].

The improved survival has been achieved through advances in several areas, including staging, MDT working, surgery, pathological reporting and also oncological treatments. Progress in medical oncology has been achieved through both advances in the efficacy of adjuvant chemotherapy and improved accuracy of disease staging, that identifies the patients who may benefit most from adjuvant treatment.

In the United Kingdom the two most commonly used staging systems for CRC are those of Dukes' and the Union for International Cancer Control (UICC) Tumour, Node, Metastases (*TNM) classification* systems[2, 3] (see appendix 1 and 2). The identification of lymph node metastases is central to both these CRC staging systems and has been integral to most staging systems since 1932 when Cuthbert Dukes modified his initial 1929 staging system to the following[2, 4],

" A cases are those in which the carcinoma is limited to the wall of the rectum, there being no extension into the extrarectal tissues and no metastases in lymph nodes, B cases those in which the carcinoma has spread by direct continuity to the extrarectal tissues but has not yet invaded the regional nodes, and C cases those in which metastases are present in the regional lymph nodes[2]"

This modification arose from survival analysis of patients with rectal cancer treated by surgical excision. It was noted that patients classified as Dukes' C under the new modification had a 3 year survival of 7% against 73% for Dukes' B and 80% for Dukes' A[2].

Although Dukes' initial staging system pertained to tumours of the rectum there have been a number of modifications since, including its use for colonic as well as rectal cancer[5]. Throughout these modifications metastatic involvement of regional lymph nodes has remained a critical feature. Similarly, the UICC TNM system also clearly identifies patients in whom there is lymph node involvement (detailed in appendix 2). The reason that nodal involvement remains such a crucial feature is its impact on a patient's likelihood of long-term cure, lymph node involvement confers a reduction in 5 year survival of 20-30%[1, 6], (see table 0-1 below). Consequently the presence of lymph node metastases usually modifies the therapeutic recommendation for a patient. Node positive patients may be offered adjuvant chemotherapy, with the expectation of a 10-15% survival benefit[7].

Table 0-1 – Percentage of cases and 5 year survival by Dukes' stage at diagnosis, colorectal cancer patients diagnosed 1996-2002 England[1]

Dukes' Stage at Diagnosis	Percentage of Cases	5 Year Relative Survival
A	8.7%	93.2%
B	24.2%	77.0%
C	23.6%	47.7%
D	9.2%	6.6%
Unknown	34.3%	35.4%

Accurate nodal stage discrimination is also important to provide patients with realistic and accurate estimates of prognosis and to allow meaningful comparative audit of outcomes between individual units. It has been shown that the number of lymph nodes harvested from a case of CRC may have an important role in accurate nodal stage discrimination[8-19]. If too few nodes are sampled it is possible that a case in which lymphatic metastases are present, although not identified, may inaccurately be assigned a node negative status. The consequence of which is under treatment and inaccurate prognostic information provided to the patient. At a unit or population level this may also worsen stage specific survival results through a phenomenon called stage migration, which has previously been described by Feinstein[20]

0.2 Stage Migration – The *Will Rogers'* Effect

"When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states."

Will Rogers 1930

Feinstein first proposed an apparent linkage between the American Humorist Will Rogers and the importance of accurate stage discrimination on improving survival in stage specific cancer in 1985[20]. Feinstein's work identified that advances in diagnostic imaging in lung cancer patients improved staging by identification of metastatic disease, which lead to an improved survival in all 'TNM' groups; the relevance in CRC patients relates to lymph node status. In a unit where lymph node harvest is optimised, it is more likely that patients will accurately be staged if node positive.

This improved stage discrimination could have the effect of improving stage specific survival of both node negative and node positive groups. If the node negative group includes patients falsely assigned to this stage (through failure to identify present nodal metastases), these patients are likely to worsen the overall stage specific survival of this group. The addition of these patients to the node positive stage may also improve the stage specific survival of this group. This is because these patients are more likely to have a lower burden of nodal disease, with associated improved survival, compared to patients

assigned to the node positive stage who may have more advanced lymphatic involvement.

0.3 Is the Number of Lymph Nodes Harvested Important?

If no lymph nodes are evaluated following surgical resection of bowel cancer, it follows that this case can never be assigned a node positive status. It is less clear on the other hand whether there are a critical number of nodes that should be examined to be certain of identifying all node positive cases. There has never been, nor is there likely to be, a randomised control trial evaluating the association between lymph node examination and survival after the surgical treatment of CRC. The highest quality available data is from two secondary analyses of multicentre randomised control trials of adjuvant chemotherapy focusing on the impact of lymph node harvest on survival[10, 21]. A summary of the results of these studies is presented in table 0-2, which shows that increasing nodal harvest is associated with improved survival.

Table 0-2 – Five year survival and disease free survival from secondary analyses of adjuvant chemotherapy RCT's

Study	Nodal Status	No Lymph Nodes	Overall 5 year Survival %	p value	Disease Free Survival %	p value
Intergroup 0089[10] (n = 3411 patients)	N0*	<11 11-20 >20	73 80 87	<0.001	72 79 83	0.11
	N1*	<11 11-40 >40	67 74 90	<0.001	65 70 93	<0.001
	N2*	1-35 >35	51 71	0.002	48 69	0.014
INTACC[21] (n=3248 patients)	Combined N0* & Node positive	0-7 8-12 13-17 >17	69 69 76 76	0.031	56 60 64 67	0.002
	N0*	0-7 8-12 13-17 >17	81 81 87 89	<0.001	66 74 77 83	<0.001
	Node positive	0-7 8-12 13-17 >17	57 59 66 63	0.3	47 48 53 54	0.11

*N stage according to TNM staging system. p values = log-rank test

The intergroup 0089 study[10] examined differing adjuvant fluoracil based chemotherapy regimens for high risk colon cancer patients, high risk was defined as node positive or node negative with the primary tumour invading the serosa or with obstruction or perforation. Rectal cancers were excluded. There were 3411 patients studied of whom 648 were node negative. The

principal finding, of this secondary analysis, was that survival was improved in both node negative and node positive colonic cancer as more lymph nodes were examined. The authors used recursive partitioning to identify the breakpoints used in their survival analysis. This demonstrated that in node negative cases survival improved unto a level greater than 20 nodes. In node positive disease survival improved until >40 nodes were examined in stage N1 disease and until >35 nodes were examined in stage N2 disease.

The second secondary analysis of the INTACC study [21] was a study of differing adjuvant fluoracil based chemotherapy regimens for patients with high risk colon cancer. High risk in this study was defined as node positive or node negative with the primary tumour invading the serosa. Again rectal cancers were excluded. The study population was 3248 patients, of whom 1635 were node negative and 1613 were node positive. In this study the breakpoints for lymph node harvest were based on quartile division of lymph node harvest of the whole study population. The principal finding of this secondary analysis was that survival of node negative cancer was dependent on lymph harvest, although in this study the number of lymph nodes harvested did not impact on survival of node positive disease.

Apart from these secondary analyses of randomised controlled trial (RCT) data there have been several population based cohort studies and single centre series that have studied the impact of nodal harvest on survival, selected results are presented in table 0-3. A study by Cserni et al[13] of 8574 node negative patients has not been presented in the table because their results were not suitable for tabulation. In this study data from the

Surveillance, Epidemiology and End Results Program (SEER) was subjected to multi-variate proportional hazards modelling to investigate impact of the number of nodes examined on survival. It was found that survival improved with increasing nodal harvest and that there was no cut off above which an increase in the number of nodes evaluated had no effect on prognosis. Another national cohort study by Vather et al.[19] has also not been tabulated due to the number of subgroups in their results. This study used New Zealand Cancer Registry data from 4309 patients with colonic cancer. Vather and colleagues divided both node negative and node positive patients into stratum of 4 node intervals up to >33 nodes (harvest = 1-4 nodes ,5-8 nodes ,9-12 nodes etc). A stepwise improvement in survival for both node negative and node positive cancer up to a level of 13-16 nodes was observed; beyond this level survival was similar irrespective of the number of nodes examined. Although both node negative and node positive groups exhibited improved survival up to the 16-node level the differences in survival between strata were more marked in the node negative than positive group. A British population based study of 3592 CRC patients by George and co-workers[22] similarly found that survival improved for both node negative and node positive disease with increasing nodal harvest, with nodal harvest stratified into three groups of 0-4 nodes, 5-10 nodes and >10 nodes.

Table 0-3. Impact of nodal harvest on survival in population based cohort studies and single centre series.

Study	Number of patients	Nodal Status	No Lymph Nodes	Overall 5 year Survival	p value
National Cancer Database, USA[11]	35 787 *Colonic only*	N0*	1-7 8-12 ≥13	49.8% 56.2% 63.4%	<0.001**
Swedish Cancer Registry[15]	3735 *Colonic only*	N0*	1-11 >11	65% 75%	<0.001
Kentucky cancer Registry[23]	2437 *Colorectal*	N0*	1-12 >12	56% 63%	<0.001**
Caplin et al[14]	222 *Colorectal*	N0 N1	<7 ≥7 <7 ≥7	49% 68% NA NA	0.001** 0.7**
Law et al[24]	115 *Colonic only*	N0*	<7 ≥7	62% 86%	0.03**
Cianchi et al[17]	140 *Colorectal*	N0*	<9 ≥9	54.9% 79.9%	<0.001**
Goldstein et al[9]	745 *Colorectal*	N0*	≤7 8-12 13-17 ≥18	62% 68% 71% 76%	0.018**
Ratto et al[12]	487 *Colorectal*	N0 N1	11.4 29.4 11.4 29.4	83% 91% 58.9% 84.2%	0.04*** 0.06***
Edler et al[16]	1025 *Colorectal*	N0 N1	0-11 ≥12 0-11 ≥12	77% 88% 54% 66%	0.02** 0.08**

* Impact on node positive patients not studied ** log-rank test

*** log-rank test, study compared different pathological techniques for lymph node evaluation with overlapping time periods, mean lymph node harvests according to technique were compared

The findings from the two secondary RCT analyses[10, 21] mirror the results of the majority of the population based studies and single centre series

previously discussed, in that nearly all studies have demonstrated a survival advantage with increased harvests in node negative disease. However, the situation in node positive cancer is far less clear with some studies demonstrating a survival advantage with increased harvests and others showing no difference.

In node negative patients it is plausible that stage migration alone could explain the improved survival observed with higher nodal harvests. However, stage migration alone cannot explain the better survival observed by some in patients with node positive disease who have higher nodal yields. It is possible that a more radical lymphadenectomy or tumour-host interaction may play a role in these patients. If the host patient is able to mount a significant immune response to the disease process there maybe reactive lymphadenopathy that makes lymph node identification easier. The consequence of which is that overall harvest improves because the nodes are easier to identify. This ability to mount an immune response may then confer a survival benefit because it signifies that the host is better able to fight off the disease process. In a recent cohort study evaluating relationship between node number and survival in colon cancer patients, patients with prominent lymphocytic infiltration in the primary tumour had a survival advantage; these patients also tended to have higher nodal counts[22].

0.4 What is an appropriate nodal harvest?

The body of published literature thus supports the view that increasing nodal harvest may optimise staging and possibly survival in the treatment of CRC. However, there is controversy in the scientific literature concerning how many nodes need to be evaluated in order to minimise the risk of under staging a patient's disease. Published recommendations range from a minimum of six nodes[14] to as many as possible[9, 13]. Following a review of the published evidence at that time (1990) the Working Party Report to the World Congress of Gastroenterology recommended that at least 12 nodes per patient need to examined following CRC excision[25]. This recommendation of 12 nodes has subsequently been endorsed by National agencies in both the United Kingdom and the United States of America[26-29]. In spite of these endorsements there is a lack of agreement as to whether obtaining increased nodal harvests actually improves outcomes[30] and whether the 12 nodes guidance is appropriate[21].

0.5 Factors Influencing Lymph Node Harvest

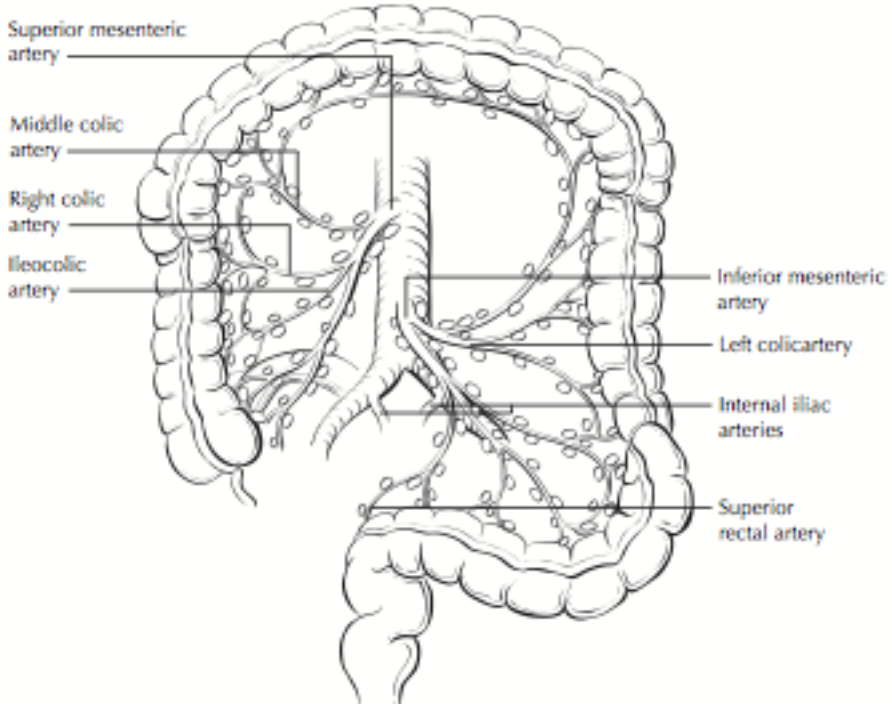
There are several factors that influence the absolute number of lymph nodes examined following surgical resection of CRC. These relate to the individual techniques of the surgeon and pathologist and factors that relate to the patients biological make up, tumour biology and type of surgical resection[31, 32]. The number of nodes present in any one patient's specimen is fixed,

however, whether they are removed or identified is reliant on the surgeon and pathologist involved in the care of that patient.

0.6 The Surgeon and Pathologist as Variables in Lymph Node Harvest

Anatomical teaching is that the lymphatic drainage of the gastrointestinal tract lies adjacent to its arterial supply. In the large intestine there are three recognised groups of nodes that drain the bowel: paracolic nodes adjacent to the bowel, intermediate nodes that lie along the main blood vessels supplying the colon and along the marginal artery and finally pre-aortic nodes (see figure 0-1). It is believed that the nodal basins drain into each other from below upwards in a sequential manner[33]. Surgical dictum has been to achieve a high proximal ligation of the principal vascular pedicle supplying the area of bowel in which a tumour is located [34]. This maximises nodal clearance and provides prognostic information because involvement of the apical nodal confers a worse prognosis[35]. It therefore follows that a less radical surgeon who fails to achieve as high a tie as possible is likely to provide a reduced yield. Following resection lymph node identification becomes the responsibility of the reporting pathologist.

Figure 0-1 The lymphatic nodes of the colon and rectum[36]



Inter-unit variation in the number of nodes examined following CRC resection is commonly reported [15, 37-45]. Different patient populations with differing pathological stage of disease treated could explain this inter-unit variation. However, comparative audit between units in close geographical proximity, managing similar disease profiles have demonstrated that significant difference between units remains[39, 46]. The implication of this finding is that differences observed, in these studies at least, must be attributable to the techniques of surgeon or pathologist or both, rather than intrinsic differences in the patients treated. Whilst inter-unit variation in lymph node harvest is frequently reported, studies examining the impact that individual surgeon and pathologist has on lymph node harvest are less frequent.

Looking specifically at the surgeon's role, it is a reasonable assumption that the radicality of surgical excision will have an impact on the available number of nodes in a specimen; if just the bowel alone, without any attached mesenteric tissue is submitted for examination then the nodal harvest is likely to be low. Some of the available literature supports the supposition that surgical performance contributes the number of nodes harvested; with the finding that two factors, higher surgeon volume and coloproctology sub-specialisation, are associated with a higher nodal harvest[47, 48]. However, these data emanate from the United States of America (USA), published United Kingdom (UK) data has found that a sub-specialist interest in coloproctology does not impact on lymph node harvest. Norwood et al published their experience in Leicester and found that the operating surgical team (colorectal specialist versus general surgeon) made no difference in the nodal harvest of 2449 patients operated on over a nine year period in their unit[49]. Another small UK series of 167 rectal cancers, in which non-specialist colorectal surgeons performed 21% of resections, found no difference in lymph node harvest between surgeons[50]. Another difference between the UK and USA is that sub-specialisation in colorectal surgery has occurred more rapidly in the UK, where a specialist colorectal surgeon now carries out almost all elective CRC resections. This specialisation would be expected to confer less variability in the radicality of mesenteric excision and therefore there should be less variability in the lymph node harvest achieved by colorectal sub-specialist surgeons.

Whilst it is believed that the extent of mesenteric resections performed in the UK are fairly standardised, the work of Hohenberger and colleagues in Erlangen, Germany, using a technique of, “complete mesocolic excision (CME)” has demonstrated that it is possible to achieve a more radical lymphadenectomy than is the current norm in the UK [51, 52]. Hohenberger et al. have been using the more radical CME for over 20 years and recently reported their results, in brief, the technique requires complete mobilization of the entire mesocolon, and high central vascular ligation[51]. Using this technique they have a median nodal harvest of 29 nodes per patient. The Erlangen group has recently performed a comparative study of their post-operative specimens against those following surgery in Leeds[52]. This study found that specimens removed in Erlangen had higher lymph node harvests (median lymph node harvest 30 in Erlangen versus 18 in Leeds), had greater mesenteric volume with a longer length of the central vascular pedicle and had longer colonic segments compared to the colorectal unit in Leeds, UK[52]. In this study survival was not an outcome measure, however, they have previously reported that their five year survival using CME is much higher than is observed in the UK[1], with a five year survival of 90% for stage I and II disease and over 70% for stage III disease[51]. These results demonstrate that more radical surgery can be expected to achieve higher lymph node harvests, provided the extra nodes resected are identified in the pathological examination of the specimen.

The impact that individual pathologists have on nodal harvests has been infrequently reported. However, whilst there is a relative paucity of published

research, it again seems reasonable to assume that the pathologist should play a significant role in the number of nodes identified from any one specimen. The literature that is available supports this hypothesis. Rieger et al, in a single surgeon series working at two separate Australian hospitals concurrently, found that the harvest achieved was significantly different at the two sites, in unit 1 (76 specimens) the median harvest was 10 nodes/patient and in unit 2 (54 specimens) 18 nodes/patient [42], the case mix in this series was similar suggesting that the difference must relate to the reporting pathologist or pathological technique. Recent data from the Dutch rectal cancer radiotherapy randomised trial of 1227 patients, found large differences in nodal yields between different units and between pathologists within a single unit with similar disease profiles[38]. In a smaller UK single unit study, of 167 rectal specimens[50], differences between pathologists were reported that was significant on both uni and multivariate analysis. Johnson et al [47], in addition to finding that surgeon volume impacted on harvest, also found that specimens that underwent gross examination by a staff pathologist had more nodes identified than those examined by residents or staff technicians. Ostadi et al [53], in a small single centre series of 264 patients, reported that multi-variate analysis of factors affecting lymph node harvest showed the pathology assistant to be the most important determinant of lymph node harvest. The mean number of nodes retrieved between assistants in this series ranged from 12.6 to 29.7 ($p<0.001$). Whilst the identity of the pathology assistant appears important in studies from the United States, this is less likely to have an impact on United Kingdom results because most specimen

dissection is carried out by medically qualified pathologists rather than technicians.

0.7 Pathological Techniques to Increase Nodal Yield

Most laboratories in the UK use a manual dissection technique to identify lymph nodes, as outlined in the Royal College of Pathologists guidance on reporting colorectal cancer, "Standards and Datasets for Reporting Colorectal Cancer (2nd edition) 2007" [28]. In summary, this recommends that nodal identification should begin with the apical node, identified by serial sectioning from the sutured vascular margin. The remaining nodes are identified by transverse slicing of the mesentry following adequate fixation. The recommendation also highlights that although a standard of 12 nodes has been set, this does not mean that pathologists should stop searching once twelve nodes are identified. This technique has been reported to be laborious and time consuming and is often delegated to a trainee pathologist, with limited experience[54].

Compared to manual dissection the technique of chemical fat clearance has been reported to increase nodal yield [32, 48, 55-59] and upstage tumours[32, 56, 58-60]. Chemical fat clearance involves chemical dissolution of the fat in the mesentry in which the nodes are embedded. Haboubi et al. [56] subjected 47 colorectal resection specimens to standard laboratory processing, followed by alcohol / xylene clearance and found that an additional 51.5 nodes / specimen were identified. This resulted in 12 out of 41 malignant cases being

upstaged. Brown et al [59] subjected 15 colonic specimens to serial dehydration in alcohol and acetone. They found that the nodal harvest rose from 20.8 to 68.8 nodes/patient, 83% of the additional nodes were <2mm. In this series finding the additional small nodes did not upstage any tumours from N0 to N1/2, however, three stage N1 cases were upstaged to N2 disease. Although finding the extra small nodes did not change any patients from a node negative to node positive stage in this series, it has previously been recognised that small nodes can harbour metastatic disease. Herrera-Ornelas et al. [61] found that 39 of 59 metastatic nodes were <5mm in size. Although some authors disagree [62], the consensus of the literature supports the view that fat clearance techniques will up-stage some tumours. The reasons why this technique have not been universally adopted are not clear but may be due to the associated extra-workload for the pathology laboratory[54].

0.8 Sentinel Node Biopsy

Since sentinel lymph node biopsy (SLNB) was first described in the treatment of malignant melanoma[63], it has become the norm in the management of many solid organ malignancies, particularly breast cancer and malignant melanoma [64, 65]. In these tumours, prior to SLNB introduction, the conventional surgical treatment was usually wide local removal of the primary tumour and a full lymphadenectomy of the primary draining nodal basin, whether or not these nodes contained metastatic disease. The sentinel lymph node (SLN) concept states that the first lymph node or nodes to receive direct

drainage from a tumour will be the first site of metastatic spread, as such if this node is free of metastatic tumour the remainder of the nodal basin will also be free of disease. In breast and melanoma surgery SNs are identified in the lymphatic basin by injection into or near the tumour of either or both aqueous blue dye and radiolabelled colloid (identified using a gamma probe). This is performed at the time of resection of the primary tumour. The identified SN is then surgically removed and subjected to histopathological assessment. If the SNs are found to be metastatic, the patient has a second operation to clear the nodal basin. If however, the SN is free of disease, the patient is spared the unnecessary morbidity of a full surgical lymphadenectomy. The potential benefits of the technique for node negative patients with breast cancer and melanoma are therefore clear and the technique has been validated as an effective and oncologically sound technique[66, 67].

Previous authors have explored the use of both in vitro and ex vivo sentinel node biopsy in the management of colorectal cancer, [68-72]. The results of in vitro sentinel node biopsy have been mixed with a few reporting excellent results[69], whilst others have experienced several difficulties, including: failure to identify the sentinel node/s in up to 40% of patients[73], false negative rates of up to 67%[74] and sensitivities as poor as 25%[75]. The reasons for these difficulties are probably multi-factorial but include the relative variability in lymphatic drainage of the colon and rectum, compared to other solid organ cancers in which in vitro sentinel lymph biopsy use has been successful. Another problem with the technique in the management of

colorectal cancer is that “skip lesions”, in which the nodes closest to the primary tumour are negative but distant nodes are metastatic, appear to occur more frequently than in other solid organ malignancies[76, 77]. In addition, the anatomy of the arterial supply to the large bowel lends itself to a standardised lymphadenectomy, whether or not nodes are involved. It would be inappropriate and technically challenging to re-operate on a patient shortly after an initial large bowel resection in order to perform a more radical mesenteric excision because a sentinel node has been found to be positive. For these reasons the usefulness of in-vitro sentinel node techniques must be questioned.

The use of ex-vivo sentinel node biopsy appears to have more promise, this is primarily because it does not alter the therapeutic treatment of the patient (the extent of surgical lymphadenectomy remains unchanged) but does allow for a more focused assessment of the sentinel node [68, 70, 72, 78], including using techniques such as ultra-sectioning, immunohistochemistry or RT-PCR analysis [54]. The use ex vivo mapping in this way has been shown to upstage up to 30% of patients initially assigned a N0 status to N1 or N2 stage disease[79, 80]. With the use of ex-vivo sentinel node biopsy, similar rates of technical failure to those of in-vitro biopsy have been observed[68, 78, 81], however, those patients in whom the technique fails can still have a conventional pathological assessment of their nodal basin.

0.9 The Patient as a Variable on Lymph Node Harvest

Lymph node harvest achieved following bowel cancer resection appears to be dependent on both the techniques of the surgeon and the pathologist. However, even if both optimise their technique is there inter patient variability? A large number of variables that relate to the patient have been purported to influence nodal yield. Patients presenting with bowel cancer will have differing demographic profiles and biological make up, differing disease stages and possibly have received differing pre-operative neoadjuvant treatments, all of these may impact on the numbers of nodes evaluated following colorectal resection.

The impact of patient gender on lymph node harvest has been studied, with mixed results [19, 40, 44, 49, 50, 53, 82-85]. Some studies have reported a statistically significant difference between the sexes, with all studies that identified a difference reporting that yields are higher in women than in men[19, 44, 53, 84, 85]. Conversely, there are several studies that have not reported a significant difference between the sexes [40, 49, 50, 82, 86]. Critical appraisal of the methodology of these studies, shows that the larger series of national cancer registry data, with between 4500 and 116000 patients, [19, 44, 85] have found that bowel cancer resection in women confers a higher nodal harvest. The majority of studies which refute this finding are single centre studies with a maximum of 2500 patients, the exception being the analysis of ACPGBI bowel cancer audit data with eight

thousand patients[40] that demonstrated no difference. The finding that the larger studies are those with a statistical difference raises the possibility that there could be a type I error. Even if this is not a manifestation of a type I error, although statistically significant differences have been reported, the actual increased harvest reported in women ranges between 0.4 and 1 node per patient, which must be considered of doubtful clinical significance[19, 84].

Most studies that have examined whether patient age influences lymph node yield have found that advancing age confers a reduced lymph node yield following colorectal resection [38, 40, 48, 49, 53, 82]. The way in which these differences have been analysed and reported in the literature varies: some studies have carried out categorical analysis, with patients age split by decades [44, 48, 87], all three of these studies reported an increased yield of three or four nodes in patients under the age of fifty, but less marked reductions between subsequent decades of between zero and one node per increased decade. Tekkis et al looked at the impact of age on harvest in patients reported to the ACPGBI bowel cancer audit using regression analysis, finding that every advancing decade conferred a reduction in harvest of 0.9 nodes/decade[40]. Similarly, Norwood et al in a series of 2449 patients from Leicester subjected their data to linear regression analysis, finding a reduction in harvest of one node for every advancing decade using linear regression analysis [49]. Whilst there is heterogeneity in the methods used in the above analyses, the homogeneity of the results strongly supports increasing age is associated with a reduced lymph node harvest. Explanations for this include the possibility that surgeons are more likely to

perform a wider lymphadenectomy in young, fit elective patients[40] or alternatively lymph nodes may involute with advancing age[88].

In the literature patient gender and age are the most frequently reported patient related variables that may impact on lymphatic harvest. Relatively few other patient related variables have been studied. Patient race has been examined, with the finding that it has no impact on harvest [44, 49, 82]. Body Mass Index (BMI) has also been evaluated, but only in studies limited to rectal tumours. Mekenkamp et al in a secondary analysis of the Dutch multi-centre radiotherapy rectal cancer found that higher BMI conferred a reduced harvest[38]. Ha et al in a smaller single centre series of rectal cancers reported that both low and high BMI reduced nodal yield[84]. In the only study that had addressed whether patient co-morbidity impacted on nodal yield, Tekkis et al. found that following multi-variate analysis patients with higher American Society of Anaesthesiologists (ASA) score (worse co-morbidity) had lower nodal yields than those classified as ASA I (see appendix 3 for definitions of ASA).

0.10 Tumour Stage and Size and Nodal Harvest

Studies that have examined whether disease stage impact on lymph node harvest have found that more advanced tumours, both in terms of stage and size of tumour, are associated with increased lymph node harvests[38, 40, 48, 50, 53, 82-84, 86, 87, 89]. The staging methods reported in these studies have been heterogeneous, with some studies using T and N staging [38, 48, 82, 86, 89] whilst others have used either the Dukes' system [40, 50] or the

AJCC system[53, 84]. Table 0-4 (page 40) summarises the findings of studies that have reported their results regarding lymph node harvest and pathological stage. All studies presented have found statistically significant differences in yield yields according to disease stage using multi-variate analysis techniques. The table only includes results suitable for presentation in a tabulated format (some published series have reported their results in graphical format not suitable for summarisation in this manner).

In addition to pathological stage, tumour size has also been found to independently affect lymph node harvest. Chou and colleagues, in the largest reported study of factors impacting on harvest, reported that for every 1cm increase in tumour size a 2-3% increased yield was observed [82]. Data from the Dutch rectal cancer radiotherapy found that harvests increased by 3 nodes between tumours measuring <2cm and 2-5cm and by a further 3 nodes from 2-5cm and >5cm [38]. Rullier et al. in a smaller single centre study of factors impacting on harvest in rectal cancer specimens found that splitting specimens into those with a primary tumour less than 4cm in size and greater than 4cm conferred an increase in yield of 6 nodes (median 12 versus 18 nodes respectively)[83].

Table 0-4 Summary of effect of pathological stage on lymph node harvest in published series

	Staging System Reported			
Study	**T stage**	**N stage**	**Dukes'**	**AJCC**
*Chou et al.[82]** (n = 153 483)	*Colon* T1 - 6 nodes T2 - 10 nodes T3 - 12 nodes T4 - 11 nodes *Rectal* T1 - 5 nodes T2 - 8 nodes T3 - 10 nodes T4 - 8 nodes	*Colon* N0 – 10 N1 – 12 *Rectal* N0 – 8 nodes N1 – 11 nodes	*Not reported*	*Colon* I - 9 nodes II - 11 nodes III - 12 nodes *Rectal* I - 8 nodes II - 9 nodes III - 11 nodes
*Baxter et al.[44]** (n= 116995)	*Not reported*	*Not reported*	*Not reported*	I – 6 nodes II – 10 nodes III – 11 nodes
Elferink et al.[87] (n=10788)	*Node negative* T1 – 5 nodes T2 – 7 nodes T3 – 9 nodes T4 – 8 nodes *Node positive* T1 – 5 nodes T2 – 8 nodes T3 – 9 nodes T4 – 10 nodes	N0 – 8 nodes N1 – 9 nodes	*Not reported*	*Not reported*
Tekkis et al.[40] (n= 8409)	*Not reported*	*Not reported*	A – 9.4 nodes B – 11.6 nodes C1 – 11.8 nodes C2 – 14.3 nodes	*Not reported*
Mekenkamp et al. [38], (n=1530)	*Node negative* T1 – 5.3 T2 – 7.1 T3 – 8.6 T4 – 9.7 *Node positive* T1 – 8.5 T2 – 10.5 T3 – 10.3 T4 – 13.7	*Not reported*	Not reported	*Not reported*
Ha et al. [84] (n=615)	*Not reported*	*Not reported*	*Not reported*	I – 15.1 nodes II – 17.7 nodes III – 18.8 nodes
Dilman et al. [48] (n=574)	T1/2 – 15.3 nodes T3/4 – 19.5 nodes	Not reported	Not reported	Not reported

* The studies by Chou[82] and Baxter[89] are both retrospective analyses of SEER data with periods of study overlapping and therefore in part contain the same patients

In addition to pathological stage, tumour size has also been found to independently affect lymph node harvest. Chou and colleagues, in the largest reported study of factors impacting on harvest, reported that for every 1cm increase in tumour size a 2-3% increased yield was observed [82]. Data from the Dutch rectal cancer radiotherapy found that harvests increased by 3 nodes between tumours measuring <2cm and 2-5cm and by a further 3 nodes from 2-5cm and >5cm [38]. Rullier et al. in a smaller single centre study of factors impacting on harvest in rectal cancer specimens found that splitting specimens into those with a primary tumour less than 4cm in size and greater than 4cm conferred an increase in yield of 6 nodes (median 12 versus 18 nodes respectively)[83].

0.11 Tumour location

Tumour location and type of surgical resection have both been found to influence nodal yield following resection. The literature can be split into studies that have examined colonic cancers only, rectal cancers only and colon and rectal cancers in the same series. Studies that have examined both colonic and rectal cancer in the same series have found the yield following rectal resection is lower than colonic resection. Chou et al. [82] in the largest reported series found that colonic resections yielded a median of 11 nodes per patient against 8 nodes following rectal resection. Ostadi et al.[53] found that rectal cancers yielded 3 less nodes than colonic tumours. Baxter et al.[44] found that right sided colonic tumours yielded the highest harvest with 11 nodes per resection against a yield of 7 nodes for left sided

colonic and 8 nodes for rectal cancer. The finding that right sided colonic resections have a higher yield than left sided is supported by other series [19, 48, 82, 85] including those that have limited their study to just colonic tumours. Analysis of New Zealand [19] and Dutch [85] cancer registry data, limited to patients with colonic disease, found that right sided resections yield 2.7 and 2 more nodes per patient than left sided tumours respectively. Analysis of 8409 patients in the United Kingdom's ACPGBI bowel cancer audit found that the highest yields were for sub/total colectomy and right hemicolectomy, with the lowest yield procedures being sigmoid colectomy (9.7 nodes), abdominoperineal excision of rectum (8.5 nodes) and Hartmann's procedure (4.9 nodes)[40]. The reasons why right sided resections provide higher yields than left are poorly understood but could relate to longer specimens and increased volume of lymph node containing mesenteric tissue around the right hemicolon.

Several series have specifically looked at lymph node harvest following rectal cancer resection [38, 83, 84, 90]. Two consistent findings are apparent in these studies; lymph node yield is lower after abdominoperineal excision of rectum (APER) than after anterior resection (AR) and use of pre-operative neoadjuvant therapy reduces nodal harvest. Data from the Dutch radiotherapy in rectal cancer trial found that APER was associated with 2.7 nodes less per patient than AR [38], Rullier et al. in a single centre 495 patient, 10 year experience of treating rectal cancer found that following multi-variate analysis APER conferred a 4.2 node less yield than AR [83]. The afore mentioned study from UK ACPGBI data reported that harvest following

APER was 2.2 nodes less than after AR [40]. In the same study use of pre-operative radiotherapy reduced nodal yield by two nodes per patient, similar numeric differences were observed in the Dutch rectal cancer radiotherapy [38]trial and in the reported by Rullier et al. [83].

0.12 Emergency presentation

In general, patients presenting as an emergency with bowel cancer do so at a more advanced pathological stage than those operated on electively[91]. It may therefore be expected that patients undergoing emergency resection may have higher harvests than their counterparts having elective surgery, given that more advanced tumours have higher nodal yields. However, few studies have addressed whether surgical urgency impacts on nodal yield. Tekkis et al.[40] in the UK ACPGBI lymph node study found, using multi-variate analysis, that emergent operations were associated with 0.8 nodes per resection less than elective procedures. Ostadi et al. [53] in a small single centre series found on univariate analysis that emergency surgery harvested less nodes, although on multivariate analysis this difference was accounted for by other co-founding variables. The only other study that investigated whether operative urgency plays a roll in harvest has found no difference between elective and emergent resections[49].

0.13 Laparoscopic surgery

Another surgical factor that could potentially impact on lymph node retrieval is laparoscopic CRC resection[92]. The technique was first described in the 1990's [93] but has only recently been popularised in the UK, partly due concerns about the oncological adequacy of the technique compared to conventional open surgery[94, 95]. One oncological concern was that it would not be possible to perform as radical an excision of the mesentry and lymph node basin by laparoscopic compared to open surgery. This was due to the perceived technical difficulty of dividing the main arterial pedicle as close to its origin as possible when a laparoscopic approach was used. However, the results of the four principal RCTs comparing open against laparoscopic colorectal resection have used lymph node harvest as an outcome measure and found no difference in the harvests achieved (results are summarised in table 0-5) [96-99]. These results were recently subjected to meta-analysis which confirmed that their was no difference in the harvests achieved [100].

Table 0-5 Comparison of the lymph node harvests in the four principal RCTs comparing open and laparoscopic colorectal cancer resection

Trial Name	Open Lymph Node Harvest (n patients)	Laparoscopic Lymph Node Harvest (n patients)	p value
Barcelona[101]	Mean 11.1 (n=108)	Mean 11.1 (n=111)	p=ns
CLASSIC[97]	Median 12.5 (n=268)	Median 11 (n=526)	p=ns
COLOR[96]	Median 11 (n=621)	Median 11 (n=627)	p=0.35
COST[99]	Median 12 (n=428)	Median 12 (n=435)	p=ns

This literature review of factors that influence lymph node harvest has shown that factors relating to the surgeon, the pathologist, the tumour, the patient and use of neo-adjuvant treatment will all impact on the harvest of any one individual patient. One chapter of this thesis will study the factors that influence lymph node yield in two colorectal Multidisciplinary Teams (MDTs) linked by the re-location of a consultant colorectal surgeon mid-way through the study period.

0.14 Harvest as a Marker of Quality in Bowel Cancer Management

The Bristol enquiry into paediatric cardiac surgery mortality [102] resulted in increased scrutiny of surgical outcomes and comparative audit in the UK. The report recommended that there, "must be agreed and published standards of clinical care for healthcare professionals to follow" and that, "there must also be a system of external surveillance to review patterns of performance over time". In the management of bowel cancer, both in the UK and the US, there has been interest in identifying outcome measures of bowel cancer treatment that are suitable markers of performance and quality to facilitate audit. Lymph node harvest has been suggested as a suitable marker[103-107]. There is a sound rationale for its use in this way[108]. Lymph node status is one of the key determinants of a patient's chance of cure and has significant impact on the use of adjuvant chemotherapy, therefore as a quality indicator harvest is of importance. Additionally, lymph node harvest may be considered to reflect the quality of both surgeon and pathologist and therefore has cross-disciplinary

importance rather than reflecting the good or bad practice of one individual. Finally, a good quality indicator should be easily found in the patients' medical record, since the publication of a minimum dataset for reporting colorectal cancer[109], nodal harvest has been found to be well reported in most units[110]. Harvest therefore has merit for use as a marker of quality, although it must be recognised that it is just one aspect of managing colorectal cancer and other measures also have merit and should not be forgotten[111].

0.15 Impact of National Guidance on Lymph Node Harvest

In the UK, guidance on lymph node harvesting following colorectal resection was issued by the National Institute of Clinical Excellence (NICE) in 2004 [26]. The guidance stated,

> *"In patients with colon cancer treated with curative intent, 12 or more nodes should normally be examined; if the median number is consistently below 12, the surgeon and the histopathologist should discuss their techniques"*

The professional bodies of the UK's colorectal surgeons (ACPGBI) [27] and pathologists (Royal College of Pathologists) [28] have issued guidance identical to NICE viz 12 lymph nodes should be harvested following colorectal resection. Similarly, the AJCC in the United States have issued a 12 node guidance [112]. On both sides of the Atlantic these guidelines have seen

increases in nodal harvests in large population studies[44, 85]. In the year that the NICE guidance was introduced the ACPGBI bowel cancer reported that the UK median harvest was 10 nodes / patient and only 35% of patients undergoing resection had an harvest that exceeded 12 nodes[107]. One chapter in this thesis will examine the impact that national guidelines and audit have had on lymph node harvests since the NICE guidelines were published[26].

Thesis Aims

The aims of this thesis are:

- To perform risk adjusted comparative audit of lymph node harvesting in a single unit and of the surgeons and pathologists who staffed the unit.

- To study factors that influence lymph node harvest following CRC resection, with particular regard to the impact of surgeon and pathologist performance.

- To study the impact that working with a different MDT, following geographical relocation, has on a surgeon's reported lymph node yield following colorectal resection.

- To study the impact that guidelines for nodal harvest and comparative national audit against guidelines have on national performance.

- To study what variables impact on five year survival following colorectal cancer resection

- To study the impact that lymph node harvest has on survival following colorectal cancer resection.

- To evaluate the use of lymph node ratio as a prognostic indicator in lymph node positive colorectal cancer

Chapter 1

Surgeon and Pathologist as variables on lymph node harvest following bowel cancer surgery

Section A – Unit comparative audit of lymph node harvest and factors Influencing lymph node yield

1.1 Introduction

Accurate staging of CRC relies on the identification of lymph node (LN) metastases. Consequently, national guidance from NICE [26], the Association of Coloproctology of Great Britain and Ireland (ACPGBI) [27] and the Royal College of Pathologists (RCPath)[28], have recommended that twelve nodes/patient are examined following colorectal cancer resection. The RCPath and ACPGBI have also recommended annual audit of a units' LN harvest.

The ACPGBI annual audit and Welsh Bowel Cancer Audits (WBCA) have reported LN harvests, as part of their national audit programme, since 2002[113]. However, one potential problem with comparative audit is that varying case mix between units, rather than differing performance may account for any observed differences. Consequently, in 2004 the ACPGBI audit team carried out multilevel multifactorial regression analysis of the factors that may have impacted on LN yield to develop a multifactorial predictive model for lymph node harvest[107]. This model uses patient and operative variables to allow units to calculate their adjusted lymph node harvest against national data, which allows adjusted comparative audit to be performed. The model is available on-line at www.riskprediction.org.uk. The ACPGBI LN model is shown in appendix 4.

1.2 Aims

The aims of this section of chapter one were, to carry out in a single MDT:

i. Comparative audit including surgeon and pathologist performance of LN retrieval against the national guidance of 12 nodes / patient, with adjustment using the ACPGBI lymph node harvesting model[107].

ii. An examination of factors that influence lymph node retrieval in surgery for colorectal cancer

1.3 Patients and Methods

The study population was 436 patients undergoing resection for adenocarcinoma of the colon or rectum, operated on in a single unit (Princess of Wales Hospital (POWH), Bridgend), between April 1999 and April 2005. All patients undergoing resectional surgery during the study period were identified form the prospectively collected ACPGBI database as part of the ACPGBI national audit. Patient and tumour data was also retrieved from this database. Individual pathology reports were retrieved from the hospital pathology database to validate the information recorded in the ACPGBI database and to identify the reporting pathologist.

All resections were carried out under the care of one of four colorectal surgeons (one of whom was appointed in the final year of the study) or one of four general surgeons with other sub-specialty interests, who staffed the unit during the study period. All cases were performed by an open technique.

All pathology specimens were reported by one of three resident Consultant Pathologists, or one of several locum Consultant Pathologists, who staffed the unit during the study period. The specimens were examined by a standard technique, which sliced the colon and mesentery at right angles to the axis of the bowel at 10mm intervals and any nodes on the upper surface were removed and sampled. The specimen was then sectioned at 5mm intervals parallel to the colonic axis (perpendicular to the first slicing) and any further nodes identified were removed and examined.

1.4 Unit comparative audit of risk adjusted nodal harvest

Data for all patients was entered into the ACPGBI LN harvesting model[107] (www.riskprediction.org.uk) to calculate individual predicted lymph node harvest (LNH), see appendix 5. Observed and predicted nodal harvest underwent logarithmic transformation to obtain the geometric mean of observed and predicted nodal harvests.

Adjusted nodal counts for each year of the study were calculated using the following formula:

$$\textit{Adjusted nodal count} = \frac{\log_{10} \textit{observed LNH}}{\log_{10} \textit{predicted LNH}} \times \log_{10} \textit{national median LNH}$$

Median LN harvests across Wales were obtained form the annual national bowel cancer reports[39, 114, 115] to calculate adjusted nodal count.

1.5 The effect of Surgeon and Pathologist on lymph node retrieval

Unit, surgeon and pathologist raw (observed) and adjusted (ACPGBI model) lymph node harvests were compared. Case mix for each individual surgeon and pathologist was also compared.

1.6 Factors influencing lymph node retrieval

The patient and operative factors collected are shown in table 2 and were studied by uni and multivariate analysis. Patients who received pre-operative

neoadjuvant therapy were excluded from analyses of pathological variables due to the uncertainty of the final pathological stages following this therapy. Sub-group analysis of patients undergoing rectal resection was also undertaken to examine any affect that the use of pre-operative neo-adjuvant therapy may have had on LN yield. Comparison between patients with inadequate and adequate lymph node harvests (< 12 and ≥12 nodes/ patient, NICE/AJCC guidance) was also undertaken.

1.7 Effect of node retrieval on the identification of lymph node metastases

Patients who had at least one lymph node metastasis underwent sub-group analysis to look for a relationship between the number of nodes examined and the likelihood of detecting a metastasis.

1.8 Statistical Analysis

The normality of distribution of the lymph node harvest data was tested with the Kolmogrov-Smirnov test, which demonstrated that the data was not normally distributed. Lymph Node Harvest for comparative audit against national performance therefore underwent logarithmic adjustment prior to comparison, as described in the methods section. Unadjusted differences in the mean number of lymph nodes harvested during surgery (with corresponding 95% confidence intervals) were calculated according to the consultant surgeon and reporting pathologist and statistical significance between individuals compared using the Kruskal-Wallis H test. Case mix between individual surgeons and pathologists was examined using a Chi-squared test. Uni-variate analysis of factors that influenced lymph node retrieval was carried out using Pearson's correlation, Mann-Whitney U test or the Kruskal–Wallis H test. Significance was assumed for all tests at the 5% level. Independent effects of variables that were significant in univariate analysis were assessed using multiple regression analysis. The effect of lymph node harvest on identification of LN metastases was assessed with Pearson's correlation and Mann Whitney U test. The data were analysed using SPSS® versions 11.0 & 16.0 for Mac statistical software (SPSS Chicago, Illinois, USA).

1.9 Results

During the study period 436 patients had surgical resection of their bowel cancer in the unit. The unit overall median lymph node harvest was 13 nodes/patient (Range 0-42, IQR 9-18, Mean 13.69 95% C.I. 13.03-14.69).

1.10 Unit Comparative Audit

The unadjusted raw results of lymph node harvest are presented in table 1-1.

Table 1-1 Unadjusted lymph node harvest by year of study

Year of Study	Number of cases	Median Harvest	IQR	Range
1999-2000	65	14	10-19	3-31
2000-2001	65	14	9-20	1-42
2001-2002	62	12	8-17	2-30
2002-2003	67	12	8-16	1-32
2003-2004	77	13	8-18	0-30
2004-2005	100	13	9-18	1-40

The Kolmogrov-Smirnov test demonstrated that the lymph node harvest data was not normally distributed (KS= 0.081, df 436, $p<0.0001$). To carry out unit comparative audit the data therefore underwent logarithmic transformation. The results of risk adjustment are presented in table 1-2.

Table 1-2 Risk adjusted lymph node harvest

Year of Study	Median Log Transformed Observed Harvest	Median Log Transformed Predicted Harvest	National Median Harvest	Risk Adjusted Median Harvest
1999-2002	13.49	9.55	9[39]*	12.59*
2002-2003	12.02	9.33	7[39]	8.70
2003-2004	12.88	9.12	9[114]	12.68
2004-2005	12.59	9.12	8[114]	10.715

* national audit of lymph node harvest was first reported in 2001-2002, the figures from this year have been used to risk adjust unit performance between 1999-2002

Unit risk adjustment of results demonstrated that unit performance was above nationally reported results. The low value of the adjusted median harvest in the year 2002-3 can be explained by the low national yield of seven nodes/patient observed in that year of study.

1.11 The effect of Surgeon and Pathologist on lymph node retrieval

The case mix of operation type for individual surgeons and pathologists is given in Table 1-3. There was no difference in lymph node retrieval between surgeons within the unit, colorectal specialists and general surgeons with other sub-specialist interests retrieved similar numbers of lymph nodes (*Kruskal – Wallis,* p=0.071, Table 1-4). However, examination of case mix demonstrated that non-colorectal specialists carried out proportionately more right sided resections (X^2 =10.087, p= 0.001), when a greater number of nodes would be expected. There was no statistical difference between the

numbers of left sided or rectal resections. There was however, a significant difference in lymph node retrieval between pathologists (*Kruskal-Wallis* p<0.001, Table 1-4). There was no difference in case mix amongst pathologists (table 1. Mean lymph node harvests and 95% confidence intervals for surgeon and reporting pathologist are shown in figure 1-1 and 1-2. Predicted harvests (ACPGBI model) for most individual surgeons were similar (between 9.3 and 9.6) with the exception of the lowest volume (newly appointed colorectal surgeon) who had a lower predicted harvest (equal to 8.0 nodes per patient). Pathologist predicted harvests were between 9.0 and 10.3 nodes per patient.

Table 1-3 Case mix for individual surgeon and pathologist

	Surgeon				
	1 (n=183)	**2** (n=104)	**3** (n=86)	**4** (n=15)	**Non CRC** (n=48)
Sub-total	3%	10%	11%	0	2%
Right Colon*	34%	34%	31%	20%	56%
Left/Sigmoid**	29%	23%	15%	20%	18%
Rectum	33%	34%	43%	60%	23%
	Pathologist				
	1 (n=215)	**2** (n=122)	**3** (n=81)	**Locum** (n=18)	
Sub-total	6%	6%	6%	11%	
Right Colon*	38%	36%	32%	22%	
Left/Sigmoid**	23%	25%	24%	22%	
Rectum	34%	34%	38%	44%	

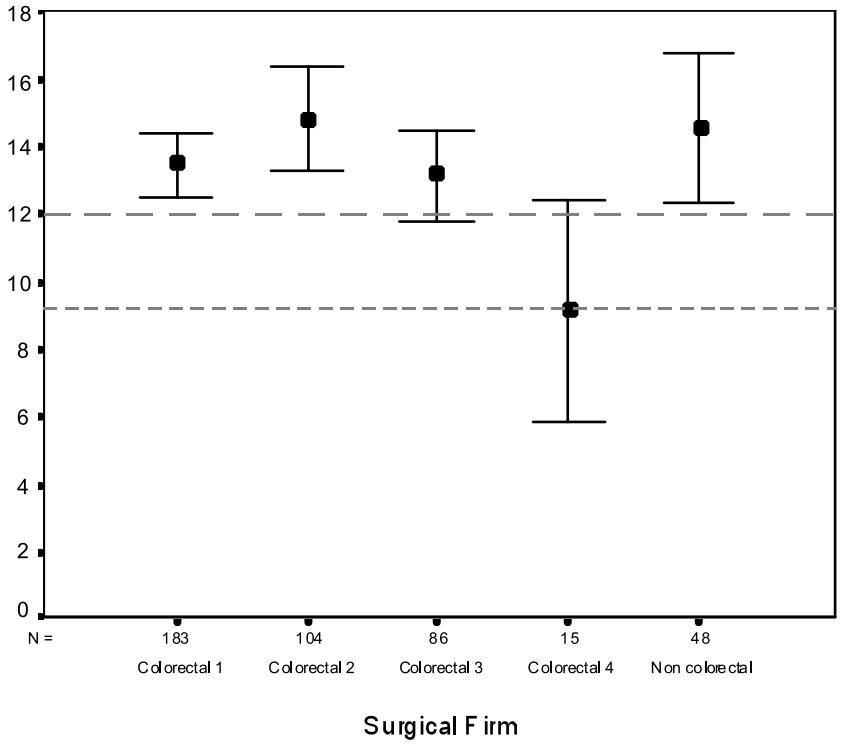
*Right Colon includes Right Hemicolectomy, Extended Right Hemicolectomy and Transverse Colectomy
** Left Colon/sigmoid includes Left Hemicolectomy, Sigmoid Colectomy and Hartmann's for non-rectal cancer

Table 1-4 Lymph node harvest by individual surgeon and pathologist

	Surgeon				
	1 (n=183)	**2** (n=104)	**3** (n=86)	**4** (n=15)	**Non CRC** (n=48)
Median LN harvest (range)	12 (1-37)	14 (1-42)	14 (0-30)	9 (2-20)	14 (1-33)
Median Predicted Harvest	9.3	9.6	9.3	8.0	9.4
					log-rank p=0.071

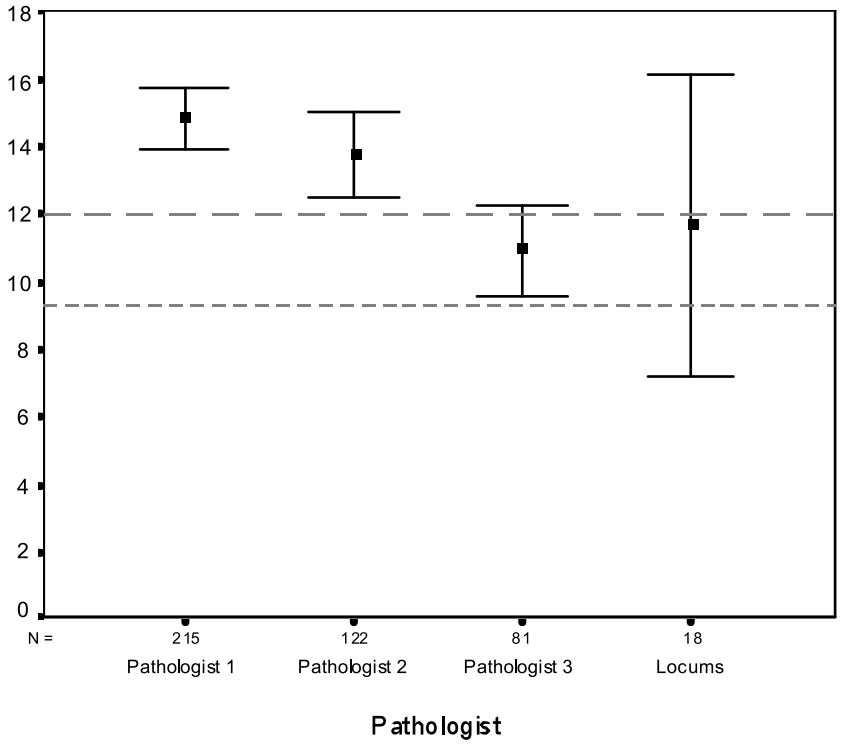
	Pathologist			
	1 (n=215)	**2** (n=122)	**3** (n=81)	**Locum** (n=18)
Median LN harvest (range)	14 (2-42)	13 (1-40)	10 (0-29)	11 (1-39)
Median Predicted Harvest	9.4	9.4	9.0	10.3
				log-rank p<0.001

Figure 1-1- Individual surgeon mean LN harvest and 95% confidence intervals



Top horizontal line equals NICE / ACPGBI / RCPath recommended minimum of 12 nodes. Bottom horizontal line is the ACPGBI model predicted harvest for the unit.

Figure1-2 Reporting pathologist mean LN harvest and 95% confidence intervals



Top horizontal line equals NICE / ACPGBI / RCPath recommended minimum of 12 nodes. Bottom horizontal line is the ACPGBI model predicted harvest for the unit.

1.12 Factors influencing lymph node harvest in colorectal cancer

Factors found to be significant determinants of LN harvest on univariate analysis were operation type, Dukes' stage, T stage and N stage of the tumour, reporting pathologist and the use of pre-operative radiotherapy in the treatment of rectal cancer (Table 1-5). In addition to the results in the table, the impact of age on lymph node yield was examined with *Pearson's correlation,* which demonstrated that age did not have an impact on nodal yields (*Pearson's* r= -0.039, p=0.442) in this study.

The factors that were significant on univariate analysis were entered into a multivariate backward linear regression model. In this model, with analysis of all patients operated on without pre-operative neo-adjuvant therapy (colon and rectal cancers), the following were found to independently predicted harvest: reporting pathologist (p=0.001), T-stage (p<0.001), N stage (p=0.011) and operative type (p<0.001). Multivariate backward linear analysis of patients undergoing resection for rectal cancer (including patients treated with pre-operative neoadjuvant therapy) demonstrated that use of pre-operative radiotherapy was not an independent predictor of reduced nodal harvest but T stage (p<0.001), N stage (p=0.001) and reporting pathologist (p=0,014) were.

Table 1-5 - Univariate analysis of factors influencing LN yield

Variable		Number	Median LN Harvest	p value
ASA*	I	82	12	
	II	200	13	
	III	127	13	p = NS
	IV	21	12	
	V	3	12	
Operation type	Right/ Extended Right Hemicolectomy	150	15	
	Transverse Colectomy	5	14	
	Left Hemicolectomy	22	13	
	Sub-total Colectomy	26	20	
	Sigmoid Colectomy	37	11	p<0.001
	Hartmann's Procedure	56	12	
	Anterior Resection	102	10	
	APER	38	11	
Operative urgency	Elective	377	13	
	Urgent	51	14	p= NS
	Emergency	8	20	
Surgical intent	Curative	349	14	
	Palliative	87	13	p = NS
Operating Surgeon	Colorectal 1	183	12	
	Colorectal 2	104	14	
	Colorectal 3	86	14	p = NS
	Colorectal 4	15	9	
	Non CR	48	14	
Dukes' stage** (pre-operative radiotherapy cases excluded)	A	41	9	
	B	166	13	
	C	175	15	p<0.001
	D	10	13	
T stage (pre-operative radiotherapy cases excluded)	1	18	9	
	2	40	11	
	3	218	14	p<0.001
	4	116	15	
N stage (pre-operative radiotherapy cases excluded)	0	205	12	
	1	100	14	
	2	87	16	p<0.001
Reporting Pathologist	1	215	14	
	2	122	13	
	3	81	10	p<0.001
	Locum	18	11	
Year of study	1999-2000	65	14	
	2000-2001	65	14	
	2001-2002	62	12	
	2002-2003	67	12	p= NS
	2003-2004	77	13	
	2004-2005	100	13	
Use of pre-operative radiotherapy in rectal cancer	Anterior Resection with***	22	8	
	Anterior Resection without***	58	11	
	APER with	18	5	p=0.003
	APER without	20	12	
	Hartmann's with***	4	10	
	Hartmann's without***	32	11	

* ASA data missing on 3 patients

** Dukes' stage clinicopathological

***Anterior resections & Hartmann's procedures carried out for non-rectal cancer excluded

1.13 Effect of node retrieval on the identification of lymph node metastases

A total of 184 patients (47.1% of cases treated without pre-operative neoadjuvant therapy) had one or more positive lymph nodes identified. This group had greater median nodal harvest than those with negative nodes (median 15 versus12 respectively, *Mann-Whitney U*= 15535, p=0.002). Differentiating the cohort into groups of patients who had 12 or more nodes assessed demonstrated that 39.2% of patients were staged as node positive (N1 or N2) following assessment of ≤ 12 nodes against 53.5% who were had > 12 nodes assessed, (x^2 = 7.926, p=0.005). Correlation between LN harvest and incidence of LN positivity confirmed that patients with higher harvests were more likely to have nodal metastases compared with patients with lesser harvests (Pearson Correlation r=0.141, p=0.005).

1.14 Summary of the Principal Findings in Section A

1. Lymph node harvests following CRC resection in this unit have been shown to exceed that of national standards using risk adjusted comparative audit against national data.

2. There was no statistical difference in lymph node harvest between the eight surgeons who staffed the unit during the study period. Case mix between surgeons was broadly similar, however non-specialist General surgeons did perform significantly more right sided resection than their colorectal sub-specialist colleagues.

3. There was a significant difference in LN harvest amongst the three pathologists within the unit. The reporting pathologist was found to be an independent predictor of LN harvest. All pathologists had a similar case mix. One pathologist had a mean harvest below the 12 node guidance and this individual's harvest was significantly lower than that of other pathologists in the unit.

4. Uni-variate analysis of patient and pathological variables that may have impacted on LN harvest demonstrated that operation type (higher yield with more proximal tumour), higher Dukes' stage, higher T stage, higher N stage and no use of pre-operative radiotherapy were associated with greater lymph node yields. On multi-variate analysis, in addition to reporting pathologist, operation type and increasing T and N stages were associated increased yields.

5. Patients with higher LN yields were more likely to have LN metastases identified.

Section B - The Pathologist as a variable on lymph node harvest – an inter hospital study

1.15 Introduction

LN retrieval is dependent on variables that relate to patient characteristics, the operation and the techniques of both the operating surgeon and reporting pathologist. Previous studies have shown inter-unit variability in lymph node harvests following surgical resection of bowel cancer[40, 44, 46]. It is not clear however, whether inter-unit variability is due to variations in patient characteristics, surgical technique or pathological technique.

1.16 Aim of Section B

The aim of this section of chapter one was to compare the LN harvests in patients undergoing CRC resection by a single surgeon, working in different MDTs, in two separate units, following geographical relocation, thereby standardising surgical technique.

1.17 Patients and Methods

The study population consisted of 213 patients undergoing consecutive potentially curative CRC resection for adenocarcinoma, operated on by a single Consultant Surgeon, in two units, over a seven year period. The surgeon moved from the Princess of Wales Hospital (POWH), Bridgend (unit 1) to Heartlands Hospital, Birmingham (unit 2) in July 2005. In unit one 110 cases were operated on between October 2002 to July 2005, and 103 cases in unit two, between August 2005 to October 2009. Patients were identified from prospectively collected databases at the two centres. Individual pathology reports were retrieved from the hospital pathology database and reviewed. All cases were carried out by an open technique and there was no change in surgical technique during the study period. All cases were either performed by the Consultant Surgeon or by a trainee under direct supervision of the surgeon. CRC screening was introduced into the second unit during the study period and eight cases performed in this unit were screen detected.

Pathological reporting of the resected specimens was performed by one of eleven Consultant Pathologists at the two units (three at unit one and eight at unit two). At the second unit, five pathologists had reported more than five specimens and the remaining three pathologists had reported less than five cases each. The results of the three pathologists reporting less than five cases were therefore pooled, totalling eight cases for analysis in this study.

Both units had broadly similar pathological laboratory standard operating policies for the retrieval of LNs from CRC specimens which consisted of: fixation in formalin, cutting through the mesenteric tissue in slices parallel to the bowel wall, followed by careful manual dissection of all LNs out of the specimen. Neither unit used fat clearing techniques.

Data recorded for each patient and compared between units included overall LN harvest and case mix assessed by comparison of patient age, site of operation (divided into right colon, left colon and rectum), operative urgency (elective or emergency), T stage (rectal cases treated with pre-operative radiotherapy were excluded in analysis of this variable) and the use of neoadjuvant radiotherapy in rectal cancer.

Factors that may have influenced LN harvest in addition to unit of operation (shown in table 1-8) were examined with univariate analysis. Significant factors on univariate examination were then assessed with multivariate analysis. Lymph node harvests, according to tumour location in right colon, left colon and rectum, were recorded and compared between units.

The proportion of LN positive (Dukes' C) cases were compared between units and the LN harvest of LN positive and LN negative cases compared within the individual units. The effect overall LN harvest had on rates of LN positive cases across the whole series was also examined.

1.18 Statistical analysis

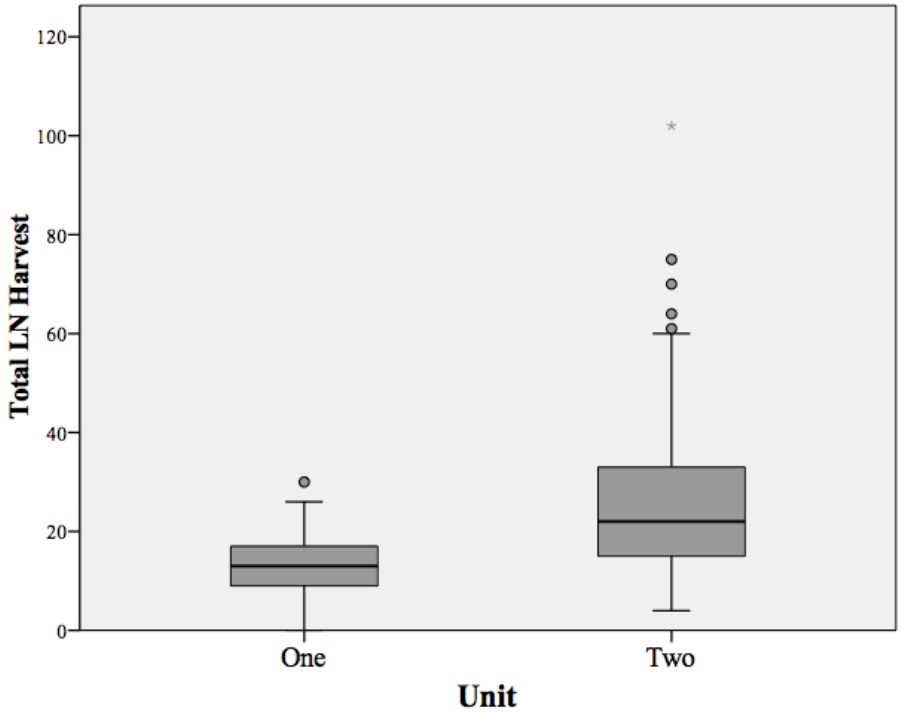
Median values were used to compare all variables. Overall LN harvest between centres was compared using the Mann Whitney *U*-test. Case mix between the units was compared with Mann Whitney *U*-test and Chi-squared test, as appropriate.

Factors influencing LN retrieval were examined with Pearson's Correlation Coefficient, Mann Whitney *U*-test and Kruskal Wallis *H*-test as appropriate. The independent effect of variables that were significant on univariate analysis were assessed using multiple backward regression analysis. Significance was assumed for all tests at the 5% level. The data were analysed using SPSS® versions 11.0 and 16.0 for Mac statistical software (SPSS, Chicago, Illinois, USA).

1.19 Results

There were 110 cases carried out in unit one and 103 cases in unit two. Overall median LN harvest was significantly different between units, unit one 13 nodes/patient (range 0-30, 95% C.I 11.7-14.0) and in unit two 22 nodes/patient (range 4-102, 95% C.I 23.0-29.6), p<0.001 (see figure 1-3).

Figure 1-3: Boxplot of Lymph Node Harvest at the Two Units



Mann Whitney
p<0.001

Figure 1-3 – Boxplots of LN harvest at the two units. Grey boxes represent the interquartile range, black horizontal line within the grey box the median LN harvest, the whiskers represent the range with circles representing statistical outliers.

Comparison of case mix, patient age, operative urgency and tumour T stage is presented in table 1-6. Case mix according to tumour site was similar between units.

Table 1-6 Case mix between units

		Unit 1	Unit 2	
		Percentage of total cases	Percentage of total cases	X^2 p value
Tumour location	Right colon*	35% (38/110)	40% (41/103)	p=0.427
	Left colon**	20% (22/110)	25% (26/103)	p=0.360
	Rectum	45% (49/110)	35% (36/103)	p=0.153
	Panproctocolectomy	1% (1/110)	0%	NA
Median patient age		72	71	p=0.789
Operative urgency	Elective	86% (95/110)	90% (94/103)	p=0.373
	Emergency	14% (15/110)	10% (10/103)	
T stage* **	1&2	21% (19/89)	20% (17/84)	p=0.857
	3&4	79% (71/89)	79% (67/84)	

* Right colon includes right hemicolectomy, extended right hemicolectomy, sub-total colectomy and transverse colectomy
** Left colon includes left hemicolectomy, sigmoid colectomy and Hartmann's procedure for colonic tumours and high anterior resection for colonic/rectosigmoid tumours
*** Rectums with pre-operative radiotherapy excluded

1.20 Comparison of LN yield according to colonic or rectal tumour location

Analysis of LN harvest according to whether the tumour was colonic (right and left combined) or rectal, demonstrated that colonic (unit one median 15 nodes vs. unit 2 median 18 nodes, p=0.014) and rectal (unit one median 10 nodes vs unit two median 31 nodes, p<0.001) were higher in the second unit. Analysis of LN harvest according to tumour location demonstrated that LN harvests were significantly higher in left colonic and rectal tumours in the second unit, but identical in tumours of the right colon (table 1-7). Intra unit analysis demonstrated unit one had higher LN harvests in colonic cases (colon median 15 nodes. vs. rectum median 10 nodes, p<0.001) whereas in unit two, higher LN harvests were observed in rectal cases (colon median 18 nodes vs. rectum 31 nodes, p=<0.001).

Table 1-7 : Lymph node harvest according to tumour location between units

		Unit 1	Unit 2	p value
		Median LN harvest/patient (range)	Median LN harvest/patient (range)	
Right colon		16 (5-26)	17 (5-47)	0.253
Left Colon		15 (6-30)	21 (4-64)	0.023
Rectum (overall)		10 (0-22)	31 (5-102)	<0.001
	Rectum without preop radiotherapy	11 (0-22) n=29	25 (21-102) n = 17	<0.001
	Rectum with pre-operative radiotherapy	7 (1-20) n=21	41 (20-70) n=19	<0.001

1.21 Factors influencing LN retrieval

Speculative univariate analysis of the factors that may have influenced overall LN harvest, at the two centres demonstrated that, in addition to the unit, significant variables for LN retrieval were: T stage and reporting pathologist (table 1-8). Age was not found to be a significant variable (Pearson's co-efficient r= -0.048, p=0.487) Backward linear regression analysis showed that unit ($p<0.001$) and reporting pathologist ($p=0.007$) were the only independently significant variables.

1.22 Proportion of cases that were Dukes' C according to unit

In unit one 46/110(42%) cases were LN positive and 49/103 (48%) in unit two, x^2 p=0.398. In unit one, the median LN harvest of patients who were LN negative was 11 nodes/patient and in those who were LN positive was 15 nodes/patient, p=0.004. In unit two the median LN harvest of node negative patients was 21 nodes/patient and, in those who were node positive, LN harvest was 23 nodes/patient, p=0.616.

Table 1-8: Analysis of factors that may have influenced overall LN retrieval

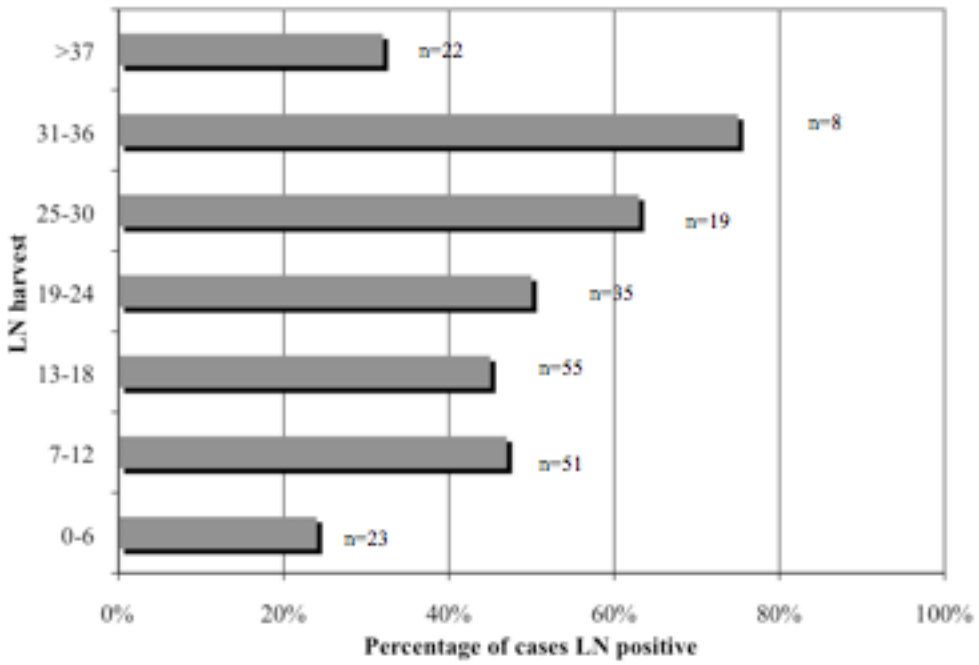
Variable			**Number**	**Median LN Harvest**	**p value**
Unit	Unit 1		110	13	P<0.001*
	Unit 2		103	22	
Operation type	Right Colon		80	16	p=0.761**
	Left Colon		48	17	
	Rectal		85	16	
	Rectal with radiotherapy		40	16	
	Rectal without radiotherapy		45	19	p=0.996*
Operative urgency	Elective		188	16	p=0.299*
	Emergency		25	15	
Final Dukes' stage	A		45	12	
	B		72	16	p=0.158**
	C		96	17	
T stage	Complete response		7	7	
	1		14	9	p=0.001**
	2		40	18	
	3		114	16	
	4		38	17	
Reporting Pathologist	Unit 1	1	31	15	
		2	39	14	
		3	40	11	
	Unit 2	4	37	33	p<0.001**
		5	32	15	
		6	12	19	
		7	8	23	
		8	6	25	
		9 ***	8	24	
Clinical presentation	Symptomatic		205	16	p=0.195
	Screen detected (all unit 2)		8	19	

* Mann Whitney U test, **Kruskal- Wallis H test
*** pooled results of 4 pathologists each reporting less than 5 cases

1.23 Effect of LN harvest on identification of LN metastases

The effect of LN harvest on the identification of LN metastases is presented in figure 1-4. Increased frequency of finding at least one metastatic node (Dukes' C) was seen up to a harvest level of 36 nodes/patient.

Figure 1-4: Lymph Node Harvest and Percentage of Cases Lymph Node Positive



1.24 Summary of the Principal Findings of Section B

1. A single surgeon who moved his place of work experienced significantly different reported lymph node harvest following CRC resection, with no change in surgical technique and similar case mix at the two units. The implication of this finding is that the difference in LN retrieval relates to the pathological technique as the surgical technique was standardised.

2. It has previously been reported that LN harvests are generally lower after rectal than colonic resections. In unit 1 proportionally more rectal resections were performed which it could be anticipated may have contributed to the lower overall harvest at unit 1. However, in unit 2, rectal cancer specimens had significantly higher LN yield than colonic tumours.

3. Higher LN yields at the second unit were associated with a higher proportion of cases being staged a LN positive, although this difference was not statistically significant.

4. Patients with higher LN yields were more likely to have LN metastases identified.

5. On multi-variate analysis unit of operation and reporting pathologist were the only independently predictive factors influencing lymph node harvest.

1.25 Discussion Chapter 1, Sections A and B

Section A of this chapter has studied lymph node harvest at a single unit (Princess of Wales Hospital (POWH), Bridgend). Risk adjusted comparative audit of unit and individual surgeon and pathologist performance was performed and analysis of factors that influenced nodal harvest following bowel cancer resection was undertaken. Section B studied the impact that relocating a surgeon from POWH to a new hospital (Heartlands Hospital (HH), Birmingham) had on nodal harvest for that surgeon (section B).

The common finding from both these sections was that reporting pathologist was an independent predictor of nodal harvest following CRC resection. The results of Section B are particularly pertinent, as they focus on the results of a single surgeon operating at two units with similar case mix, thereby standardising the surgical technique. The implication of this finding is that the difference in LN retrieval between units relates to the pathological techniques. The finding that a surgeon working at two centres can have differing harvest at each centre has only previously been reported once[42], however, in this series multivariate statistical analysis was not used as was used in the present study.

A potential explanation for the observed difference in LN harvest between POWH and HH in section B is the separate chronological time periods that the harvests cover, i.e. POWH, years 2002-5 and HH, years 2005-9. During the latter period, national nodal harvests across the UK have improved[103, 105,

116]. However, the results in section A showed that the median harvest at POWH between 1999-2005 was 13 nodes/ patient. Re-audit of harvests at POWH for the period 2006-2007 showed that the median harvest was identical, at 13 nodes/patient[117]. Audit data on lymph node harvest in HH is unavailable for the time period when the surgeon was located in POWH. However, the unchanged harvest at unit one during both time periods suggests that the national trend of increasing LN yields has not impacted significantly on the individual surgeons' results reported in this chapter.

The median nodal harvest of 13 nodes / patient at POWH reported for the period 1999-2005 (section A) are higher than observed elsewhere in Wales over similar time periods[39, 114]. In section A, use of the ACPGBI lymph node model[107] to perform risk adjusted comparative audit has shown that the higher harvest in POWH are as a result of better performance at the unit, compared with other units in Wales, rather than the alternative explanation of a more favourable case mix. It is noteworthy that the risk adjusted harvests of POWH appear very low, this is due to the low national harvests in this time period. The ACPGBI model[107] was calibrated using data national lymph node harvest data up to 2004, the results in this chapter together with the national increase in harvests [103, 105, 116, 118] suggest that this model under predicts harvest and should be revised in light of changing clinical practice.

It has previously been reported that lymph node harvests can be significantly increased by fat clearance techniques[55-57, 59]. Neither unit studied in this

chapter used fat clearance techniques. A review of laboratory standard operating policies at both units showed there was no discernable difference in methods of specimen fixation or dissection. This suggests that the intra unit differences in harvest between pathologists in section A and the inter unit differences in section B are attributable to the techniques of the individual pathologist rather than those of individual hospital laboratories.

Lymph node harvests have been reported to be lower after rectal than colonic resection [53, 82]. the results in section A of this chapter support this finding. This difference between rectal and colonic lymph node yields could explain some of the lower LN harvest observed at POWH in section B, where proportionally more rectal resections were performed. However, in HH, rectal cancer specimens had significantly higher LN yields than colonic tumours. In addition, use of pre-operative radiotherapy for rectal cancer treatment has been widely reported to reduce nodal harvests [38, 40, 89, 119] and was observed to do so at POWH in section A of this chapter. However, results from HH (in section B) show that radiotherapy use did not impact on nodal retrieval at this unit. The likely explanation, for these apparent divergences from the norm, is that a pathologist with a particular interest in rectal cancer specimens reported most of the rectal cases at HH. This pathologist has a declared specialist interest in rectal cancer reporting and has recorded some of the highest lymph node harvests for rectal cancer specimen reporting in the literature[120].

Lymph node (LN) harvests are being suggested as surrogate markers of surgical quality in the treatment of bowel cancer [8, 111]. The results in this chapter highlight the potential strengths and weaknesses of this. The results have shown that nodal harvest is not just dependent on the technical skill of the surgeon but is also strongly dependent on the pathologist, which as a quality marker in bowel cancer care has the advantage that it measures the performance of more than one individual within an MDT. However, if the focus is on "surgical" quality, an underperforming pathologist could unfairly cause a surgeon to be labelled as underperforming, without reasonable foundation. The results of colorectal surgeon four in section A emphasize another problem with using harvest as a quality indicator. This individual had a lower harvest than their other colorectal specialist colleagues, although the difference was not statistically significant. However, this surgeon was newly appointed and only carried out 15 resections in the study period, of which a far higher proportion were rectal resections that conferred a lower yield in POWH. This highlights the importance and potential danger of comparing results of simple numbers without risk adjustment that allows for case mix. In the case of colorectal surgeon four, risk adjustment identified that their expected harvest should be lower than their counterparts.

In this chapter use of multi-variate analyses of the factors that predicted lymph node harvest found that in addition to reporting pathologist in section A operation type, T and N-stage predicted harvest and the unit of operation was the only other independent predictor of harvest in section B. These factors have all previously been found to influence nodal harvest as discussed in the

introduction section of this thesis. The reasons why more pathologically advanced tumours and proximal site of tumour predicted higher harvests in section A but not in section B are not clear. It is possible that this represents a type II error, as the number of patients analysed in section B is smaller. It may also relate to the influence of the pathologist with a special interest in rectal cancer specimen reporting in HH, whose high harvests following rectal cancer resection may have skewed the results of harvest and tumour site in section B. This individual's personal series has found that in his hands more pathologically advanced tumours do not confer an increased yield, as is commonly reported in the literature [38, 40, 48, 53, 82-84], but are associated with larger lymph nodes [120].

The finding in both sections of this chapter, that patients with higher nodal harvests were more likely to have nodal metastases, is supported in previous studies [9, 121, 122]. Routine histological examination of nodes usually consists of a single slice through the identified node. This process examines less than one percent of the nodal tissue in a 5mm lymph node [123]. Previous authors have looked at the technique of ultra-sectioning nodes and have found that this significantly increases the identification of nodal metastases [124, 125]. The finding in section B of this chapter that increased nodal yield at HH was associated with a trend towards a higher proportion of cases being staged as Dukes' C further supports the potential benefit of optimising a patient's harvest. Although this difference was not statistically significant it is possible that this represents a type II statistical error and that a larger data set may yield a statistically significant result. Although

recommendations are that a minimum of 12 nodes per patient be examined, it is probably appropriate that as many nodes as possible be examined [54], supported by an increase of nodal metastasis identification up to 36 nodes in this chapter.

1.26 Conclusions Chapter 1

The results of risk adjusted comparative audit of lymph harvest against national data in this chapter suggest that the ACPGBI lymph node model under-predicts lymph node harvest and may need revision in light of changing clinical practice and improved national results. The results presented also suggest that as many nodes as possible should be examined after colorectal cancer resection to minimise the risk of under staging a patient's disease. This chapter has also confirmed reporting pathologist to be a critical determinant on the number of lymph nodes harvested following colorectal cancer resection. This has implications for the use of lymph node harvest as a marker of "surgical" quality.

Chapter 2

Impact of national audit against national guidelines on lymph node retrieval following colorectal cancer resection

2.1 Introduction

The ACPGBI bowel cancer audit project evolved from large population audits in Wessex [126], Trent and Wales [127] and Scotland [128]. Lead clinicians from these audits developed a minimum dataset that started national audit of patients with bowel cancer in 2000. In 2003 the ACPGBI audit became known as the National Bowel Cancer Audit Programme (NBOCAP). The ACPGBI and NBOCAP audits have produced annual reports since 2002. The early reports focused on producing a risk adjusted mortality model to allow comparative audit of mortality rates following surgery between units [104]. Subsequent reports have focused on other outcome measures, including lymph node harvest. Data on Welsh patients has contributed to the national audits. In addition, the colorectal steering group, part of the Cancer Services Co-ordinating Group (CSCG) in Wales has published separate audit reports including just Welsh patients.

In 2004 NICE identified lymph node yield as a quality control indicator in colorectal cancer surgery [26]. It recommended that if a units' median harvest was consistently below 12 nodes per patient, "the surgeon and pathologist should discuss their techniques". In 2005, the colorectal CSCG for Wales, following this NICE guidance, agreed lymph node harvest against this guidance would be one of its quality indicators that would be reported in subsequent annual Welsh Bowel Cancer Audit reports.

Prior to the NICE guidance in 2004 observed lymph node harvests in the ACPGBI NBOCAP national audits had consistently been below the recommended level of 12 (see table 2.1). The situation in Wales over the same time period was reported in a separate Welsh Bowel Cancer Audit (WBCA) reports [39, 114]. At this time the WBCA reports documented that Welsh node harvests were lower than those observed UK wide (table 2.1)

Table 2.1 – National and Welsh Lymph (CSCG) Node Harvest prior to implementation of NICE / CSCG Guidance

UK ACPGBI / NBOCAP National Reports				
National Report	**Period covered by report**	**Number patients reported**	**Median (range) LNH**	**% with harvest ≥ 12 nodes/patient**
2002 report[113]	Apr 1999 - Mar 2001	n=3461	11 (0-69)	27.5%
2004 report[107]	Apr 2001 – Mar 2002	n=6823	10 (0-72)	32.8%
2005 report[129]	Apr 2002 – Mar 2003	n=7439	10 (0-130)	35.5%
2006 report[105]	Apr 2003 - Mar 2004	n=6215	NA*	41.0%
CSCG Welsh Reports				
1st Welsh Report[39]	Apr 2001 - Mar 2002 Apr 2002 - Mar 2003	n=1157 (Apr 2001- Mar 2003)	8 (NA*) 7 (NA*)	NA*
2nd Welsh Report[114]	Apr 2003 - Mar 2004	n=783	9 (0-119)	NA*

***Data not included in the published report

2.2 Aim of Chapter 2

To investigate the impact of national audit on the national guidelines for lymph node harvest in surgical treatment of colorectal cancer in Wales.

2.3 Patients and Methods

The study population was all patients undergoing colorectal cancer resection in Wales, whose data on lymph node harvest had been submitted for analysis as part of the annual Welsh Bowel Cancer Annual Audit between 2005-09. During this period there were several adjustments to the configuration of Trust and Healthcare Networks in Wales. It was therefore decided to carry out all analyses in this chapter on an individual hospital multi-disciplinary team basis, as these have remained constant over the study period. All 13 Welsh MDTs that treat bowel cancer submitted data. In 2005–06 Ysbyty Glan Clwydd were unable to participate in the audit but did so in the years 2006-09. Eleven MDTs used Cancer Network Information System Cymru (CANISC) to collect and submit their data between 2005-7. Between 2005-7 Gwent Healthcare NHS Trust collected information in an ACCESS® database, which was merged with the CANISC data into a single all-Wales spreadsheet for analysis. The data for this time period was collected on a Trust basis, which included two MDTs and therefore data from the two Gwent MDTs for this period is reported separately. From April 2007 all thirteen MDTs used CANISC to record data.

Patient anonymised data was extracted from CANISC and the Gwent Healthcare ACCESS® database used by the central CANISC team. It was made available for analysis as an Excel® password protected spreadsheet (Microsoft Corporation) for analysis. The analysis was undertaken using SPSS® for Mac version 16.0.

The following were calculated on an annual basis: data quality for lymph node harvest, defined as the number of patients undergoing surgical resection that involved mesenteric excision who had their nodal harvest recorded. All Wales annual median and inter-quartile range of lymph node harvests were calculated and compared using the *Kruskal-Wallis H test.* Individual unit median harvests were calculated for the four consecutive years since following the introduction of the twelve node guidance. The number of units meeting national guidelines was calculated and the proportion of the audit population whom had a harvest of equal to or greater than 12 nodes was calculated and compared using the *chi-squared test.* For all statistical analyses significance was assumed at the 5% level.

2.4 Results

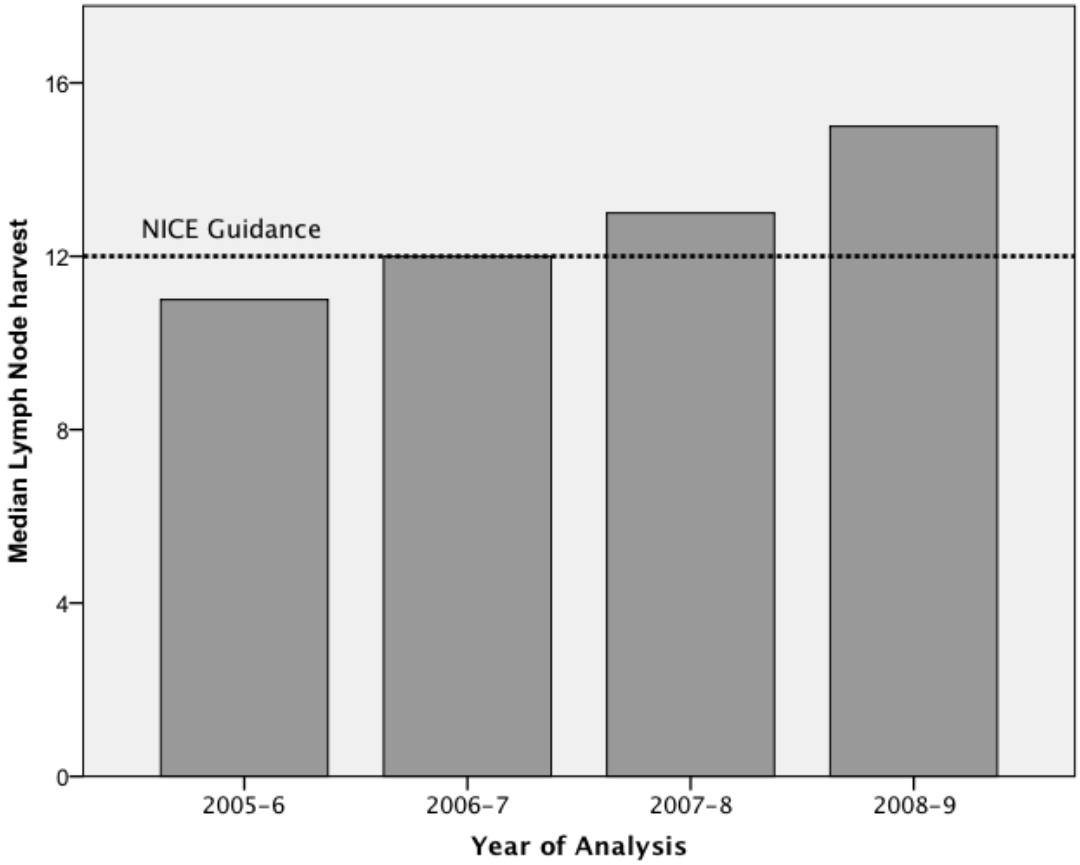
The study population consisted of 6829 patients who were treated for bowel cancer in Wales between 2005 and 2009. Of these patients 68.7% (4677 patients) were treated by a surgical procedure that included mesenteric resection and an associated lymphadenectomy. Data on lymph node harvest was available for analysis in 4036 (86.3%) of this group (table 2.2). There was year on year variation in the number of cases although the percentage of cases having a resection remained similar, as outlined in table 2.2.

Table 2.2 Population of audit by year of study

Audit Period	Total patients in audit	Total patients having mesenteric resection	Number of patients having mesenteric resection with node harvested recorded
2005-06	1452	986 (67.9%)	887 (89.9%)
2006-07	1691	1153 (68.%)	868 (75.2%)
2007-08	1793	1216 (67.8%)	1053 (86.5%)
2008-09	1893	1322 (69.8%)	1228 (92.9%)
Total	6829	4677 (68.5%)	4036 (86.3%)

The annual lymph node harvests in the Welsh Audits are presented in the figure 2.1 below. Harvests in 2005/6 were initially below the national guidance of 12 but met this standard in 2006/7. A significant year on year increase in national lymph node harvest has been observed. (*Kruskal –Wallis H test* $p<0.001$). The results of individual units are presented in the bar chart, figure 2.2, again annual improvements are observed.

Figure 2.1 Annual all Wales lymph node harvest

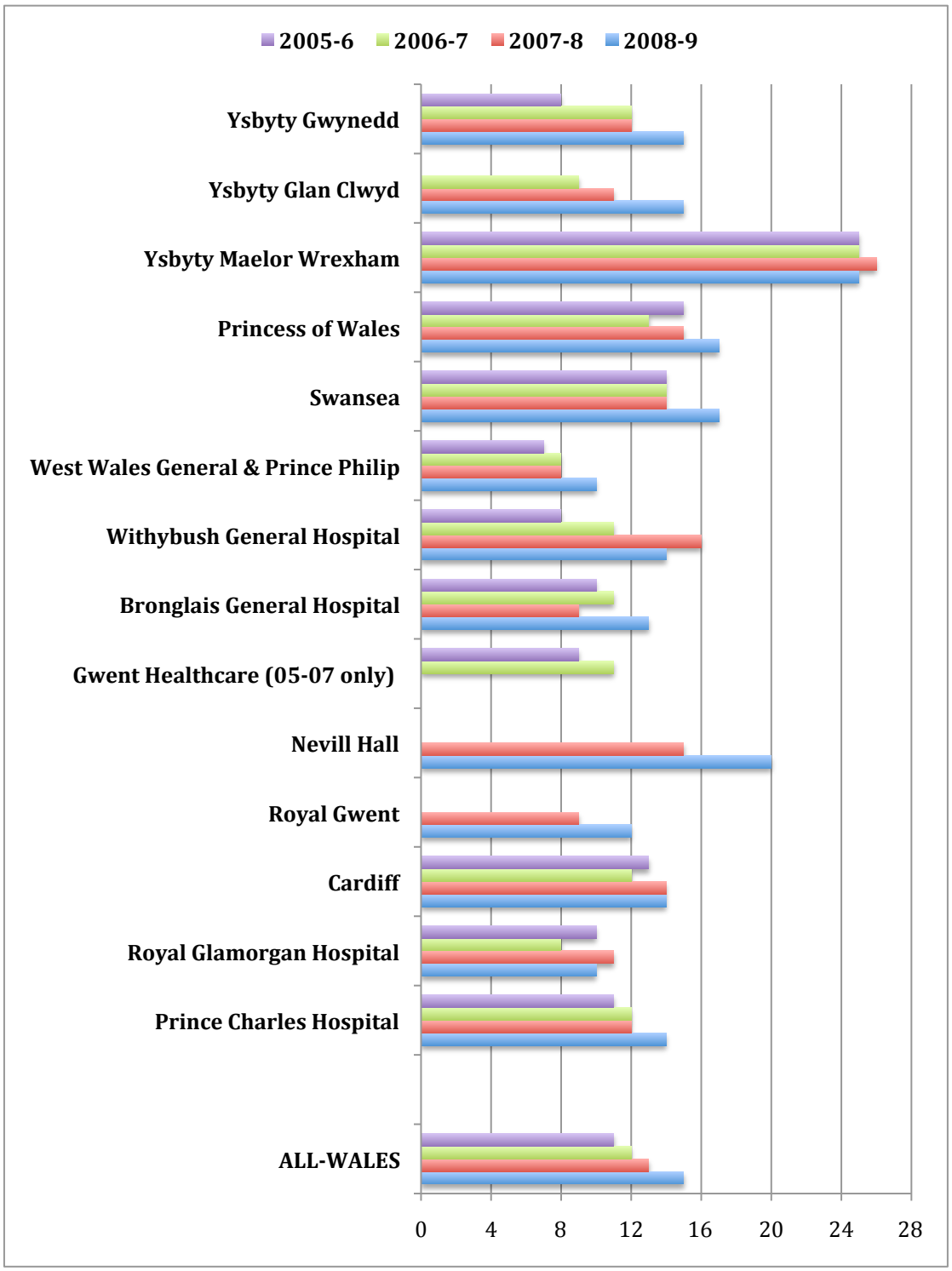


Kruskal-Wallis H test p<0.001

Year	2005-6	2006-7	2007-8	2008-9
Median Harvest	11	12	13	15
Inter-Quartile Range	6-16	5-17	9-20	10-20

Figure legend 2.1 - Bar chart showing median harvest by years of audit. Dotted reference line corresponds to NICE guidance of 12 nodes. Data table presented beneath graph.

Figure 2.2. Bar chart showing median lymph nodes examined in each trust and all Wales for audit years 2005-09.



The number of units achieving the 12 node guidance has again increased annually (figure 2.3a). Immediately after the NICE guidance was issued less than 40% of units were compliant, this has risen to more than 80% in the most recent time period. The proportion of patients having resectional surgery who had a lymph node harvest ≥12 nodes have also shown a year on year incremental rise from 49% in 2005/6 to 69% in 2008/9 (figure 2.3b).

Figure 2.3a Bar chart of the proportion of units achieving the NICE guidance of a median harvest of 12 nodes / patient. Figures within the bars correspond to the actual number of units in each category.

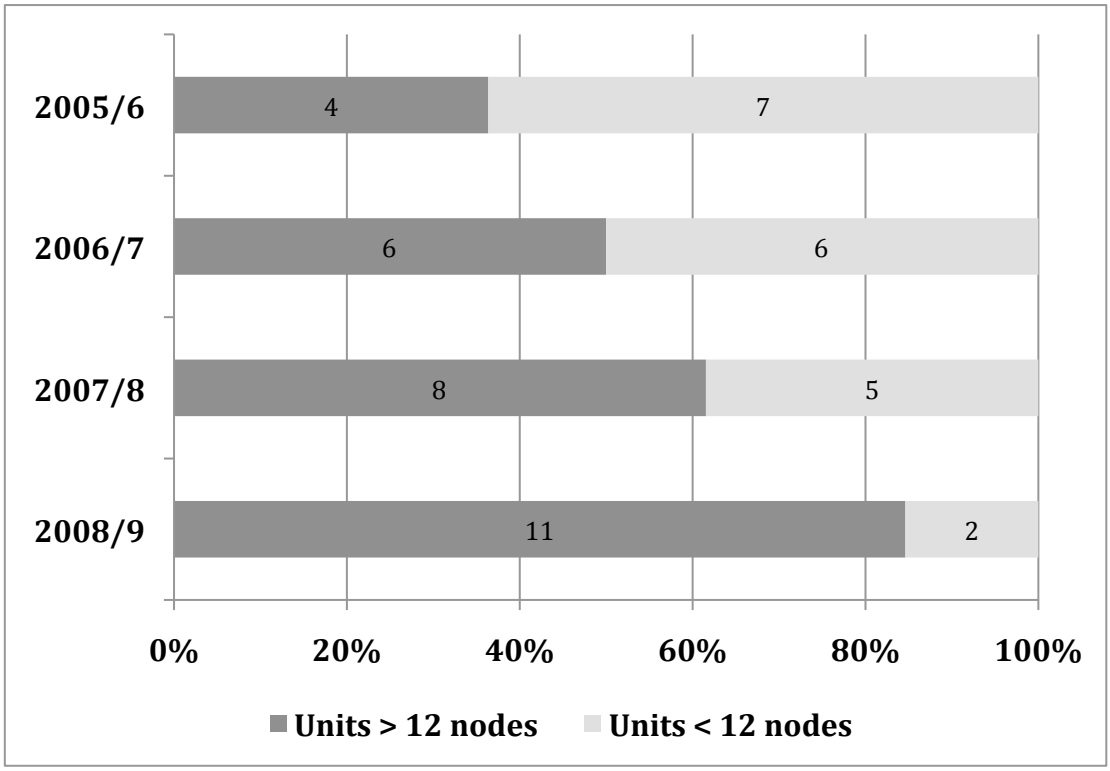
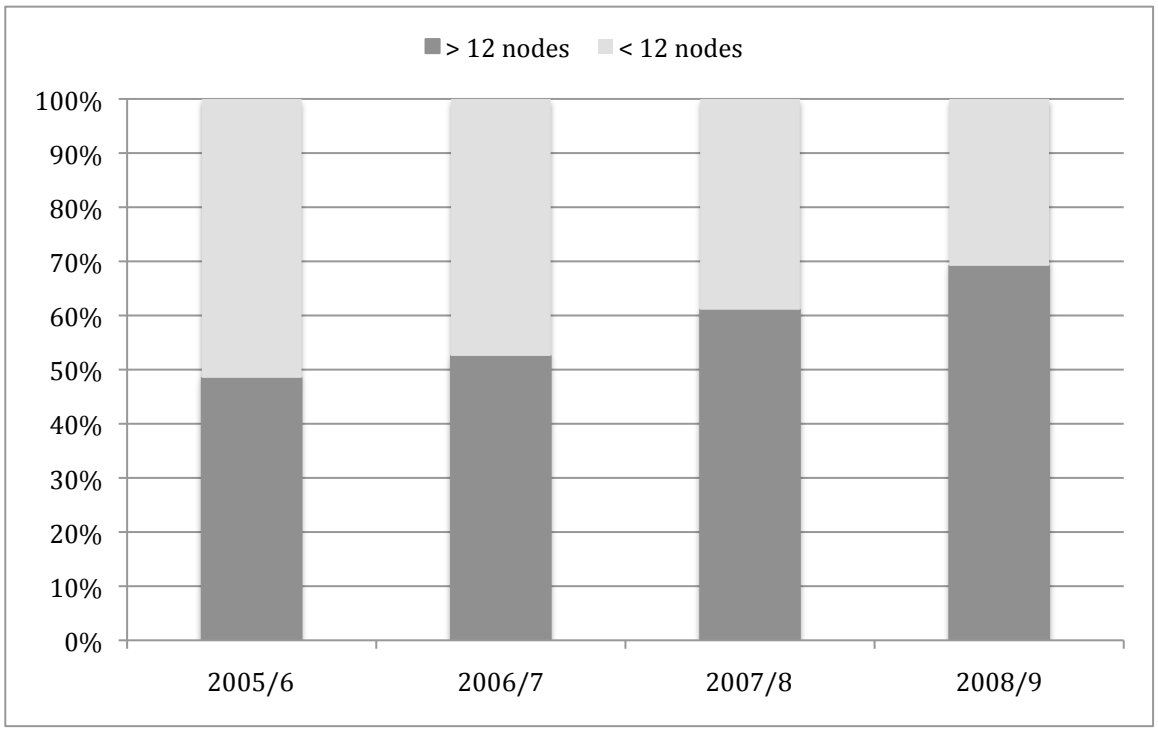


Figure 2.3b Proportion of whole audit population having greater than or equal to 12 nodes examined by year of audit. Data table presented beneath the chart.



Audit year	2005/6	2006/7	2007/8	2008/9
% Patients with ≥ 12 nodes (n)	48.5% (430/887)	52.2% (456/868)	61.1% (643/1053)	69.2% (823/1190)

2.5 Principal Findings of Chapter 2

1. The quality of data pertaining to lymph node harvest following CRC resection in the Welsh National Bowel Cancer has improved over the four year study period.

2. Median national lymph node harvests have improved from non-compliance with NICE guidance in 2005/6 to a position where median national harvests exceed the guidance, with year on year improvement observed.

3. At individual MDT level most units have shown year on year increase in nodal harvests and the number of units compliant with the national guidance has increased.

4. The proportion of patients undergoing surgical resection who have $\geq$ 12 nodes examined have increased during the study period.

2.6 Discussion

The use of clinical audit to improve performance in health care was first recognised in the 19th century by Florence Nightingale. During the Crimean war (1853-1855) Nightingale was appalled by the unsanitary conditions and high mortality rates amongst injured soldiers at the medical barracks in Scutari. She, with her team of nurses, improved hygiene and sanitation. During this period she kept meticulous records of the outcomes of soldiers treated and recorded a reduction in mortality from 40% to 2%. These records were instrumental in overcoming resistance of British doctors to the improvements in sanitation and hygiene that Nightingale instituted. This success is recognised as one of the earliest programs of clinical audit improving outcomes.

In 1863 Nightingale had returned to London and commented that comparative audit was necessary to improve outcomes in healthcare across the city, however she also acknowledged the difficulties of data collection [130],

"in scarcely any instance have I been able to obtain

hospital records fit for any purpose of comparison"

*(*Nightingale 1863)[130]

In the one hundred and forty years that followed Nightingale's publication little progress was made with establishing national databases on which comparative audit could be performed. However, the Bristol Enquiry into

Paediatric Cardiac Surgery Mortality changed this. The subsequent report [102] of this enquiry made several recommendations including that there, "must be agreed and published standards of clinical care for healthcare professionals to follow" *and* that, "there must also be a system of external surveillance to review patterns of performance over time".

Since the Bristol enquiry the number of national databases for the purpose of comparative audit have increased dramatically, incorporating many aspects of healthcare, with cancer management and surgical outcomes the most commonly audited areas [131]. Whilst there are a large number of databases covering wide variety of conditions, there have been problems with the quality of data being entered, both in terms of missing data and its accuracy [131-134].

The UK wide NBOCAP audits [103, 105, 107, 113, 118, 135] have experienced problems with poor data completeness across all variables examined in the audit. In these national audits overall data quality has improved with time but there remains inter-unit variability and overall completeness of submissions is lower than the authors desire. In Wales, the CSCG have sponsored annual WBCA reports that have reported ever increasing data completeness in recent years[39, 115, 116, 136]. A significant factor promoting data collection in Wales was the issuing by the Wales Assembly Government of the Welsh Health Circular [WHC(2008)054] that mandated the use of CANISC for data collection by trusts. The data completeness for nodal harvest reported in this chapter reflects this

mandation of data collection, with 93% of patients undergoing a resection in Wales having their nodal harvest recorded in the most recent audit period.

There are other reasons why the data submitted to recent WBCAs has been more complete than in the NBOCAP/ACPGBI national counterparts. The number of trusts involved has allowed a more individual approach in Wales. Over this period, if initial analyses have shown missing data, lead clinicians of MDTs have been contacted to request improved data and the re-submitted data has been re-analysed to produce the final WBCA reports. This process of requesting improved data is almost certainly one reason why the Welsh data is more complete than the NBOCAP / ACPGBI national counterpart. Experience from the UK cardiac surgery audit has shown that a process of validation, monitoring and feedback can improve data quality [137]. In this paper Fine et al. [137] carried out a retrospective study of the data recorded in the database, which was then cross referenced with the data available from the patients' case notes, finding that data was missing in 25% of database entries compared to 1% in the patient notes. Units were then given feedback of missing data, which improved subsequent data submissions to a point where only 9% of submissions missing [137]. Whilst it is believed that the request for improved data from MDTs with poor submissions in the WBCA has been important in improving data quality, there are other potential influences that may have improved performance. There have been several educational meetings organised by the Welsh CSCG. These meetings have been attended by both cancer services clerical staff and clinicians. At these

meetings the need for improved data quality has been frequently highlighted which has potentially raised awareness of the need for high quality data.

Compliance with National Guidelines

Prior to the NICE nodal guidance in 2004 [26] nodal harvests in the both the ACPGBI / NBOCAP and WBCA audits were consistently lower than the 12 node guidance. The data presented in this chapter has shown that in the first year after the guidance the median harvest for the whole of Wales was 11 nodes/patient. At the same time the majority of units in Wales also had a median harvest below 12. In the second year after the guidance the target harvest was achieved in Wales. Thereafter there has been an annual increase in both median harvests for the whole of Wales and the number of units and patients having 12 or more nodes examined. The results of Ysbyty Maelor Wrexham presented in this chapter are also worthy of further comment, this unit has consistently achieved a median nodal harvest in excess of 25 nodes. Following personal communication with this units MDT it is believed that this is due to the diligence of a single pathologist.

There are several plausible reasons to explain the national improvement observed. The very existence of national guidelines for the number of nodes to be harvested probably has contributed to this improvement. Data from analyses of the United States SEER data mirror the findings of this chapter; that harvests increase when guidelines are introduced. An analysis of the United States SEER data between 1988 and 2000, pre-dating the 2001

National Cancer Institute (NCI) guidance that 12 nodes should be examined in node negative disease [29], found that the most common number of lymph nodes assessed in colon cancer was zero and that the median harvest was nine nodes [138]. Since the NCI guidance was published, a similar analysis of SEER data [82], which included patients diagnosed up to 2005 showed that the mean number of nodes sampled in both colonic and rectal cancer has increased dramatically. In the UK the NBOCAP audits have reported similar improvements in nodal harvest since the introduction national guidance[103, 105, 107, 118]. These results, in conjunction with the results presented in this thesis, support the hypothesis that National Guidance can improve clinical performance, although it must be acknowledged that this evidence in circumstantial.

The existence of the WBCA itself may have contributed to the improved harvest reported in this chapter is. In the paper, "Principles for Best Practice in Clinical Audit" published by NICE [139], audit has been defined as,

"a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria. Aspects of the structure, processes, and outcomes of care are selected and systematically evaluated against explicit criteria"[139]

The WBCA reports have been published on the world wide web on the CSCG website and each MDT has been sent a copy of the report and encouraged to undertake an internal review of performance against national

standards and other units in Wales. The audit results are now trust identifiable, trusts were made aware that open reporting would take place and this may have contributed to the improved results. In addition, the results of the WBCA have been publicised at the CSCG sponsored educational meetings throughout Wales. Whilst there have been no specific actions taken against Trusts failing to comply with the 12 node guidance, the CSCG for Wales highlighted its perceived importance by including nodal harvest as one of its key, "clinical indicators of bowel cancer care" in its 2005-2007 report [115].

The Bristol enquiry [102] has led to a dramatic increase in clinical audit within the UK. A Cochrane review published since the Bristol enquiry [102] examined the effect of audit and feedback on healthcare outcomes, it concluded that audit can be effective in improving clinical practice [140]. Relating this to the improvements in nodal harvests reported in this chapter, it is likely that the annual completion of the audit cycle through the existence of the WBCA may have impacted on the increased harvests reported in this chapter.

The role of feedback on practice was studied in a systematic review reported by Mugford et al. [141]. One of the findings of this review was that minimising the time interval between collection of data collection and reporting results was important in improving performance. Whilst the WBCA reports annually, there is a time lag between completion of data collection and publication of the report, typically at least 12 months. The effect of this

publication time lag is that year on year improvement may not be directly attributable to the previous years audit results. However, the consistent improvement in yield over the four years presented in this chapter suggests that the improved performance may in part be due to the effect of audit. This is supported by the results of a recent study from Canada [142], which reported that dissemination of audit results showing suboptimal harvest improved performance in a single health district.

Whilst the introduction of national guidelines and the effect of audit may both have influenced the increase in nodal harvests observed, there are other potential factors that should to be considered. "Lymph node harvest" in colorectal cancer treatment as a topic of research has become relatively fashionable in the colorectal literature. If the phrase, "lymph node harvest colorectal cancer" are entered into Pubmed [143] for the period 1st January 2004 to 31st December 2010 fifty eight citations are returned, an identical search for the preceding six year period 1st January 1998 to 31st December 2003 returns twelve citations. This increase in publications pertaining to lymph node harvest may have increased clinician awareness to the potential importance of harvest, which in turn may have influenced practice to increase nodal yield.

The improved harvests may also be influenced by the results of sub-group analyses of large chemotherapy trials. These have identified inferior survival when a node negative status is assigned on the basis of examination of less than 12 nodes confers worse survival [144]. Consequently it has been

recommended that patients assigned a node negative status on the basis of sampling less than 12 nodes should be considered 'high risk' and as such be considered for adjuvant chemotherapy [144-147]. This guidance, in the author's experience, is often the subject of debate in the colorectal MDT meeting, which frequently culminates in a request for the pathologist to search for more nodes. Whilst difficult to quantify this internal pressure from within MDTs may also have contributed to increased nodal harvests.

Sub-specialisation in surgery has been associated with improved outcomes [148-151]. It is therefore possible that the increasing surgical sub-specialisation in coloproctology has contributed to the increased harvest. Data from the US supports this hypothesis where increasing surgeon volume [47] and colorectal fellowship training [48] can confer higher nodal yields than those achieved by low volume non-colorectal surgeons. Whilst this may have impacted on the results in the US, fundamentally there are differences in the way in which sub-specialisation has occurred in the UK, compared to the US. In the UK almost all General Surgeons now have a sub-speciality interest, in which most of the elective surgery performed by that surgeon is carried out. In the US this sub-specialisation has not occurred as rapidly. Publications emanating from UK units, with similar study time periods to this chapter, and the data in chapter one of this thesis have concluded that sub-speciality of operating surgeon does not independently impact on lymph node harvests [40, 49]. Whilst data about the sub-speciality of the operating surgeon is unavailable from the WBCA, it is not believed that sub-

specialisation has had a marked impact on the results presented in this chapter.

2.7 Conclusion Chapter 2

The principal findings of this chapter are that the WBCA has experienced an annual improvement in data completeness, unit and national nodal harvests and compliance with national guidelines. The reasons for this improvement are not fully understood but could include publication of national guidelines, national comparative audit, open reporting and increased research into nodal harvests following colorectal resection. The relative importance of each of these factors on the improved performance is not known but it is likely that the reasons are multi-factorial with each factor contributory.

Chapter 3

Impact of nodal harvest on survival following colorectal cancer resection in Wales

3.1 Introduction

The rationale for maximising the number of lymph nodes harvested following colorectal resection for cancer is the perception that lower lymph node harvests risk of under-staging a patients' disease. Previous studies of node negative colorectal cancer patients (Dukes' stage A and B) have found that lower lymph node harvests are associated with worse survival[10, 12, 16, 21, 23, 38]. The situation in patients with node positive disease (Dukes' stage C) is less clear, with some studies reporting worse survival at lower harvest levels[10, 12, 16], whilst others have found no difference[14, 21, 38].

3.2 Chapter Aims

The aims of this chapter were:

i. To examine the impact that nodal harvest had on survival of patients with Dukes' stage B and C colorectal cancer in the WBCA

ii. To establish variables that independently predicted survival in Dukes' stage B and C colorectal cancer in the WBCA

3.3 Patients and Methods

The study population was the 1453 patients diagnosed with bowel cancer in Wales between April 2005 and March 2006, whose data had been reported to CANISC and populated the WBCA audit report for that year [115]. This year was chosen for this analysis because all patients who remained alive had completed a minimum of five year follow up from the date of diagnosis at the time on analysis. In this period twelve of the thirteen MDTs in Wales that treated bowel cancer participated in the WBCA. Death data was obtained by linkage of three databases: CANISC, ONS (Office for National Statistics) and WICSU (Welsh Cancer Intelligence Surveillance Unit) using NHS number as the common identifier. WICSU receives death certificate data from ONS. In May of 2011 WICSU provided survival data for all relevant CANISC patients and used NHS numbers to provide an anonymised excel spreadsheet.

Patients treated without surgical resection were excluded from analysis, as they did not undergo a lymphadenectomy, leaving 1035 patients who had undergone surgical resection with associated mesenteric resection. Potential inaccuracies in Dukes' stage reported to the audit were identified and amended in the following way; patients identified as having liver or lung metastases on their staging CT scan result had their Dukes' stage amended to stage D, irrespective of what stage had been recorded in the field "clinico-pathological Dukes' stage", twenty-five records were amended in this way. Dukes' stage D patients were then excluded from survival analyses, in total 67 patients undergoing surgical resection were Dukes' stage D, leaving 967

patients for further analysis. The aim of this study was to compare survival of patients staged as Dukes' B and C, therefore patients staged as Dukes' A were excluded (125 patients). Rectal cancer patients treated with pre-operative long-course chemoradiotherapy, which may have altered pathological stage, were also excluded (10 patients). In a further 122 patients no data on Dukes' stage or lymph node harvest data had been submitted to the audit, even though they were recorded as having had resectional surgery, these patients were therefore also excluded. This left 711 patients for analysis.

3.4 Statistical analysis

The median harvest and inter-quartile range (IQR) of patients with Dukes' stage B and C cancer was calculated and compared with the *Mann-Whitney U test.* The survival of all patients with Dukes' stage B and C colorectal cancer was calculated, using life table analyses, and compared with the *log-rank* test. The impact of lymph node harvest on survival of patients with Dukes' stage B and C disease, with variable lymph node harvests, was compared sequentially using the *log-rank* test. Speculative univariate analysis of variables reported to the audit, which may have impacted on survival, was performed on all patients with Dukes' stage B and C together, on patients with stage B only and on patients with stage C only using *log-rank* tests. In addition in Dukes' stage C patients lymph node ratio was calculated for all patients, except for the 19 patients (5.2%) who did not have data on the number of positive lymph nodes submitted to the audit. Survival was compared between the lymph node ratio groups. Lymph node ratio was defined as the total number of involved nodes divided by the total number of nodes harvested. Factors that were significant variables for survival on uni-variate analysis were then entered into a backward multivariate *cox-regression* model to determine factors that independently predicted survival in each group. Significance for all calculations was assumed at the 5% level ($p < 0.05$). Data was collected on a Microsoft Excel® (Washington, USA) and analysed using SPSS® for Mac version 18.0 (New York, USA).

3.5 Results

There were 344 Dukes' stage B and 366 stage C patients in the study with a median follow up of 69 months in surviving patients. The overall median lymph node harvest was 12 nodes per patient (IQR 8-17). Median harvest for Dukes' stage B patients was 11 nodes (IQR 7-16) and for Dukes' stage C was 12 nodes (IQR 8-18), *Mann-Whitney U* p=0.014. The Kaplan-Meier plots of overall survival in Dukes' B and C patients are presented below in fig 3-1.

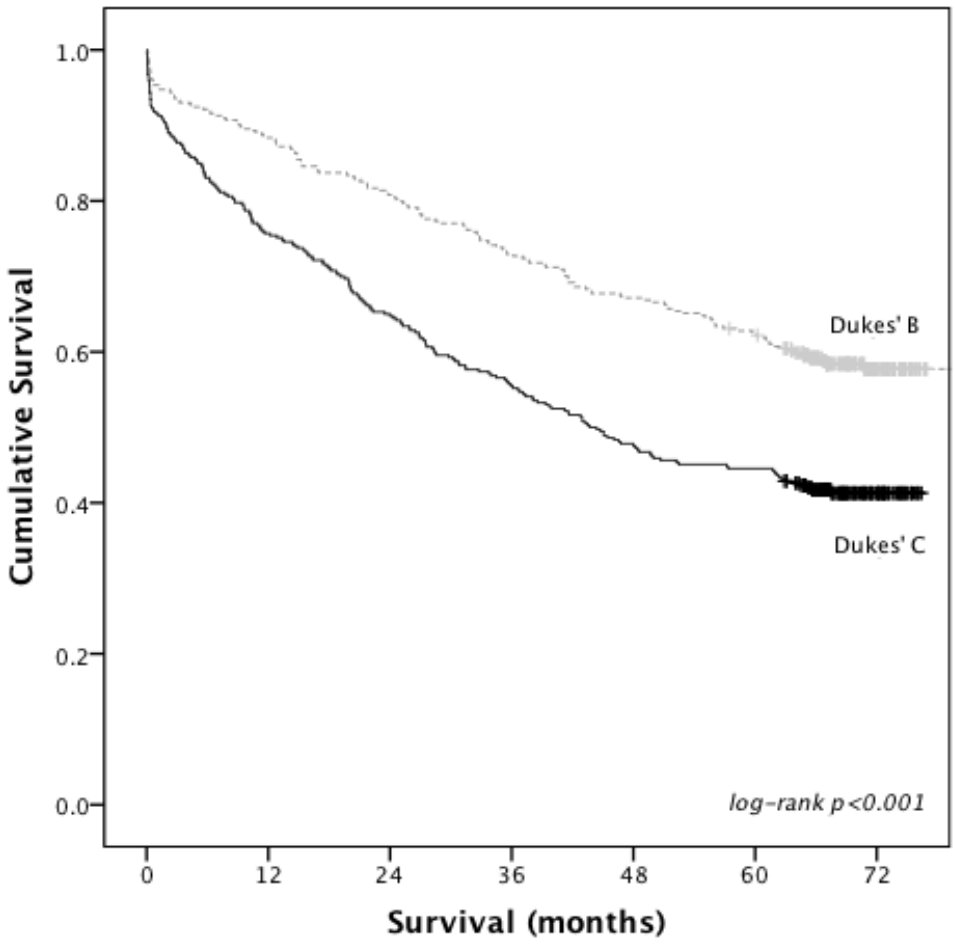


Figure 3-1 – Overall survival of Dukes' stage B and C patients

The overall five-year survival of Dukes' stage B patients was 62% against 45% in those staged as Dukes' stage C, *log-rank* $p<0.001$. Survival was then compared between Dukes stage B, divided into sub-groups sequentially according to their lymph node harvest (Table 3-1). Identical analysis was then carried out for stage C patients. In patients staged as Dukes' B, a statistically significant survival difference was observed when the cohort was split between harvests of <9 / ≥9 incrementally up to <14 / ≥14 nodes. Below and above these levels there was no statistical difference in survival. In patients staged as Dukes' C survival differences were observed when the cohort was spilt between < / ≥7 and < / ≥8 nodes. Above this level no difference in survival was observed.

Table 3-1 – Survival comparison of patients with Dukes' stage B and C disease with a variable lymph node harvest

Dukes' stage and harvest	n patients	Five year survival	*Log rank*
B ≥7 LN	272	63%	p=0.186
B <7 LN	72	58%	
B ≥8 LN	256	63%	p=0.265
B <8 LN	88	60%	
B ≥9 LN	233	65%	p=0.029
B <9 LN	111	55%	
B ≥10 LN	214	66%	p=0.011
B <10 LN	130	55%	
B ≥11 LN	191	68%	p=0.008
B <11 LN	153	56%	
B ≥12 LN	167	70%	p=0.003
B <12 LN	177	56%	
B ≥13 LN	143	69%	p=0.012
B <13 LN	201	57%	
B ≥14 LN	131	70%	p=0.017
B <14 LN	213	57%	
B ≥15 LN	114	68%	p=0.078
B <15 LN	230	60%	
B ≥18 LN	77	69%	p=0.075
B <18 LN	267	60%	
C ≥7 LN	310	47%	p=0.001
C <7 LN	56	28%	
C ≥8 LN	289	47%	p=0.011
C <8 LN	77	33%	
C ≥9 LN	265	45%	p=0.605
C <9 LN	101	42%	
C ≥10 LN	246	46%	p=0.304
C <10 LN	120	40%	
C ≥12 LN	213	47%	p=0309
C <12 LN	153	41%	
C ≥15 LN	146	43%	p=0.559
C <15 LN	220	45%	
C ≥18 LN	109	44%	p=0.897
C <18 LN	257	45%	

3.6 Variables impacting on survival of all Dukes' stage B and C patients

Speculative uni-variate analyses of factors, which may have impacted on the survival of the whole cohort, are presented in table 3-2.

Table 3-2 Uni-variate analyses of factors that may have impacted on survival of the whole study population

Factor		Data Quality*	5 year survival	*Log-rank p* value
Age	<50	100%	70%	p<0.001
	50-59		64%	
	60-69		63%	
	70-79		47%	
	>80		37%	
Sex	Male	100%	50%	p=0.163
	Female		57%	
Unit of operation	1	100%	48%	p=0.370
	2		60%	
	3		52%	
	4		54%	
	5		55%	
	6		56%	
	7		53%	
	8		49%	
	9		52%	
	10		52%	
	11		57%	
	12		54%	
NCEPOD mode of surgery	Elective	92.3%	61%	p<0.001
	Scheduled		57%	
	Urgent		42%	
	Emergency		38%	
ASA**	I	43.5%	74%	p<0.001
	II		59%	
	III		44%	
	IV		24%	
	V		No patients	

* Data Quality defined as the percentage of patients with data for this variable submitted to the audit

** ASA = American Society of Anaesthesiologists Grading System

Table 3-2 continued overleaf

Table 3-2 (continued) - Uni-variate analysis of factors that may have impacted on survival of the whole study population

Factor		Data Quality*	5 year survival	*Log-rank p* value
Type of operation	Right Hemi	100%	48%	
	Left Hemi		55%	
	Sigmoid colectomy		53%	
	Anterior Resection		66%	p<0.001
	APER		54%	
	Hartmann's		30%	
	Total colectomy		52%	
Colonic or rectal	Colonic	100%	54%	p=0.220
	Rectal		58%	
Number of nodes examined	0-6	100%	46%	p=0.027
	7-12		53%	
	13-18		55%	
	18+		58%	
Number of nodes involved	1-3	100%	57%	
	4-6		35%	
	7-9		34%	p<0.001
	10-12		27%	
	12+		34%	
T stage	T1	81.3%	100%	p<0.001
	T2		68%	
	T3		61%	
	T4		32%	
Dukes' stage	B	100%	62%	p<0.001
	C		44%	

* Data Quality defined as the percentage of patients with data for this variable submitted to the audit

** ASA = American Society of Anaesthesiologists Grading System

Factors found to have a significant impact on survival ($p<0.05$) on uni-variate analysis were entered into a backward *Cox – regression* multivariate model to determine factors independently predictive of survival. The following factors independently predicted survival:

- Advancing age (Hazard ratio 1.038 per decade increase, 95% C.I 1.028-1.049, $p<0.001$)

- Number of positive lymph nodes (Hazard ratio 1.091, 95% C.I 1.060-1.032, p<0.001)
- Number of lymph nodes examined (Hazard ratio 0.981 per node, 95% C.I 0.968-0.995, p=0.006)
- Emergency operation (Hazard ratio 1.006, 95% C.I 1.001 – 1.010, p=0.011)
- Higher Dukes' stage (Hazard ratio 1.294, 95% C.I 1.040-1.731, p=0.02)
- Higher T stage (Hazard ratio 1.003, 9.5% C.I 1.001-1.005, p=0.042).
- ASA grade (p=0.939) and type of operation (p=0.466) were excluded from the model and did not therefore independently predict survival.

3.7 Variables impacting on survival of Dukes' stage B patients only

Speculative uni-variate analyses of factors, which may have impacted on survival of Dukes' stage B are presented in table 3-3.

Table 3-3 Uni-variate analyses of factors that may have impacted on survival of Dukes' stage B patients

Factor		Data Quality*	5 year survival	*Log-rank p* value
Age	<50		No patients	
	50-59		70%	
	60-69	100%	70%	p<0.001
	70-79		61%	
	>80		45%	
Sex	Male	100%	56%	p=0.022
	Female		69%	
Unit of operation	1	100%	45%	
	2		50%	
	3		59%	
	4		61%	
	5		65%	
	6		62%	p=0.760
	7		57%	
	8		48%	
	9		57%	
	10		58%	
	11		63%	
	12		49%	
NCEPOD mode of surgery	Elective	93.9%	69%	
	Scheduled		63%	p<0.001
	Urgent		58%	
	Emergency		43%	
ASA**	I	43.6%	87%	
	II		63%	
	III		51%	p<0.001
	IV		22%	

* Data Quality defined as the percentage of patients with data for this variable submitted to the audit

** ASA = American Society of Anaesthesiologists Grading System

Table 3-3 continued overleaf

Table 3-3 (continued) Uni-variate analyses of factors that may have impacted on survival of Dukes' stage B patients

Factor		Data Quality*	5 year survival	*Log-rank p* value
Type of operation	Right Hemi	100%	58%	
	Left Hemi		63%	
	Sigmoid colectomy		62%	p=0.166
	Anterior Resection		72%	
	APER		63%	
	Hartmann's		43%	
	Total colectomy		63%	
Colonic or rectal	Colonic	100%	61%	p=0.573
	Rectal		63%	
Number of nodes examined	0-6	100%	59%	
	7-12		56%	p=0.049
	13-18		65%	
	18+		74%	
T stage	T1	79.4%	No patient T1N0	
	T2		44%	p=0.001
	T3		70%	
	T4		47%	

* Data Quality defined as the percentage of patients with data for this variable submitted to the audit

** ASA = American Society of Anaesthesiologists Grading System

Factors found to have a significant impact on survival ($p<0.05$) on uni-variate analysis were entered into a backward *Cox – regression* multivariate model to determine factors independently predictive of survival. The following factors independently predicted survival of Dukes' stage B patients:

- Advancing age (Hazard ratio 1.447 per decade increase, 95% C.I 1.307-1.802, $p<0.001$)
- NCEPOD mode of surgery (Hazard ratio 1.001, 95% C.I 1.000 - 1.002, $p<0.001$)

- Number of lymph nodes examined (Hazard ratio 0.973 per node increase, 95% C.I 0.949-0.997, p=0.003)
- Female patient gender (Hazard ratio 0.604, 95% C.I 0.477-0.949, p=0.009)
- ASA grade (p=0.237) and T stage (p=0.190) were excluded from the model and did not therefore independently predict survival.

3.8 Variables impacting on survival of Dukes' stage C patients only

Speculative uni-variate analyses of factors, which may have impacted on survival of patients staged as Dukes' C are presented in table 3-4.

Table 3-4 Uni-variate analyses of factors that may have impacted on survival of Dukes' stage C patients

Factor		Data Quality*	5 year survival	*Log-rank p* value
Age	<50	100%	58%	p<0.001
	50-59		60%	
	60-69		57%	
	70-79		34%	
	>80		28%	
Sex	Male	100%	45%	p=0.634
	Female		45%	
Unit of operation	1	100%	43%	p=0.346
	2		80%***	
	3		44%	
	4		49%	
	5		50%	
	6		41%	
	7		31%	
	8		43%	
	9		46%	
	10		39%	
	11		45%	
	12		44%	
NCEPOD mode of surgery	Elective	90.7%	52%	p<0.001
	Scheduled		52%	
	Urgent		27%	
	Emergency		32%	
ASA**	I	43.3%	63%	p=0.012
	II		56%	
	III		37%	
	IV		25%	
	V		No patients	

* Data Quality defined as the percentage of patients with data for this variable submitted to the audit

** ASA = American Society of Anaesthesiologists Grading System

*** Only 5 cases were Dukes C in this unit and 4 survived long-term

Table 3-4 continued overleaf

Table 3-4 (continued) Uni-variate analyses of factors that may have impacted on survival of Dukes' stage C patients

Factor	Data Quality*	5 year survival	*Log-rank p* value	
Type of operation	Right Hemi	100%	40%	
	Left Hemi		47%	
	Sigmoid colectomy		46%	
	Anterior Resection		60%	p=0.002
	APER		47%	
	Hartmann's		21%	
	Total colectomy		31%	
Colonic or rectal	Colonic	100%	42%	p=0.039
	Rectal		52%	
Number of nodes examined	1-6	100%	29%	
	7-12		49%	p=0.007
	13-18		45%	
	18+		47%	
Number of nodes involved	1-3	100%	53%	
	4-6		35%	p<0.001
	7-9		35%	
	10-12		27%	
	12+		25%	
Lymph Node Ratio	0 - 0.24	94.8%	51%	
	0.25 – 0.5		46%	p<0.001
	0.51 – 0.75		41%	
	0.76 – 1.0		11%	
T stage	T1	83.1%	50%	
	T2		75%	p<0.001
	T3		51%	
	T4		24%	

* Data Quality defined as the percentage of patients with data for this variable submitted to the audit

** ASA = American Society of Anaesthesiologists Grading System

*** Only 5 cases were Dukes C in this unit and 4 survived long-term

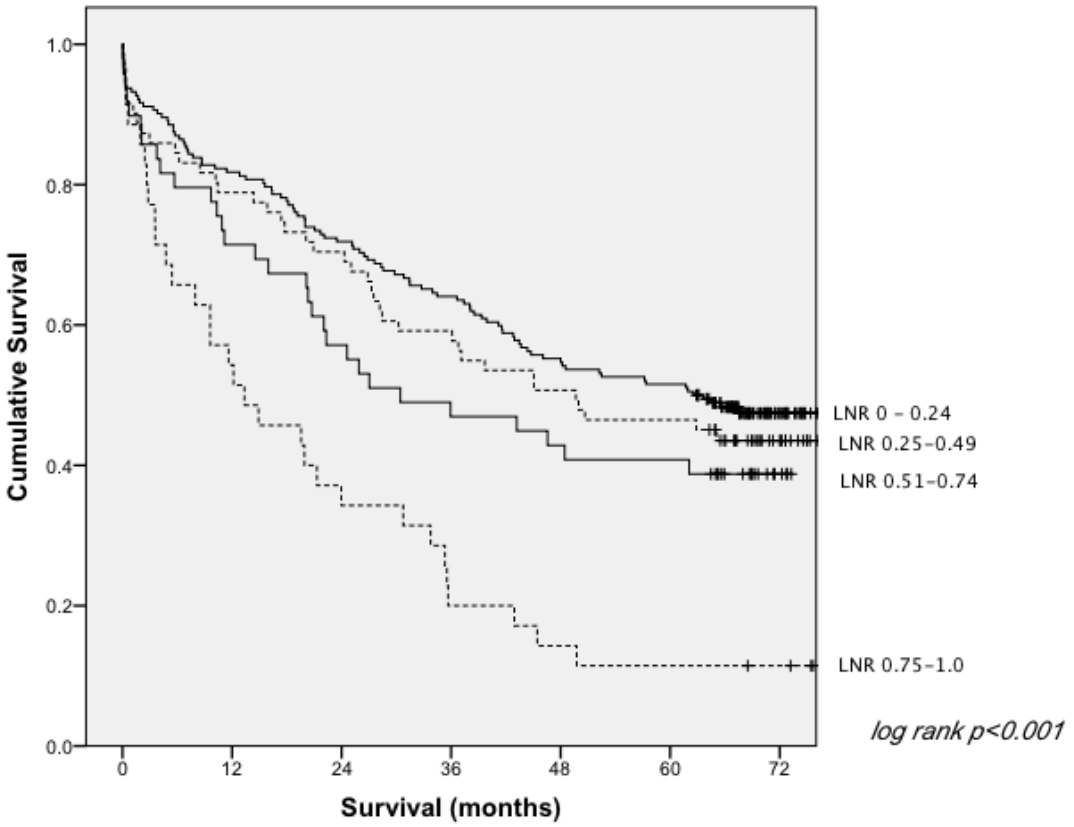
Factors found to have a significant impact on survival ($p<0.05$) on uni-variate analysis were entered into a backward *Cox – regression* multivariate model to determine factors independently predictive of survival. The following factors independently predicted survival of Dukes' stage C patients:

- Advancing age (hazard ratio 1.036/ decade (95% C.I - 1.023-1.050), p<0.001)
- Lymph node ratio, defined as the number of involved lymph nodes divided by the total lymph node harvest, (hazard ratio 1.308 (95% C.I – 1.195 – 1548, p<0.001).

Number of involved nodes, number of lymph nodes examined, ASA grade, operation type, NCEPOD mode of surgery, tumour site and T stage were excluded from the model and did not therefore independently predict survival.

The Kaplan – Meier curves of survival according to lymph node ratio are presented in figure 3-2 and demonstrate the poor prognosis of patients with higher LNR.

Figure 3-2. Kaplan-Meier plot of survival according to LNR (lymph node ratio)



Data table supporting figure 4-2

LNR	Number at risk Survival (months)					
	0	12	24	36	48	60
0 - 0.24	191	157	138	122	105	99
0.25 - 0.49	70	56	49	41	36	33
0.5 - 0.74	48	35	28	23	21	20
0.75 - 1.0	34	19	12	7	5	4

3.9 Discussion

This chapter has studied the factors that have impacted upon survival of patients, with Dukes' stage B and C colorectal cancer (CRC), treated in Wales between April 2005 and March 2006. The principal findings, in relation to this thesis, are that five year survival in Dukes' stage B (node negative) cancer is independently predicted by higher nodal harvests and that lymph node ratio (number of involved nodes: total node harvest) independently predicts survival in Dukes' stage C (node positive) cancer.

The overall five year survival of patients with Dukes' stage B disease treated in Wales in the study period was 62%, this is lower than the 77% five year survival reported for patients diagnosed in England between 1996-2002[1]. The 45% five year survival of Dukes' stage C patients in this chapter, however, is similar to the 47% reported in England between 1996-2002[1]. Worse survival for Welsh patients with bowel cancer, compared their English and European counterparts, has previously been reported [152]. However, why this difference is so marked in stage B disease reported in this chapter is not known.

Patients staged as Dukes' stage B in this chapter had a significant survival advantage at higher harvests when the cohort was split between harvests of <9 / $\geq$9 incrementally up to <14 / $\geq$14 nodes, with improved five year survival of between 10 and 14%. These data support the findings of previous studies that have similarly found that lower harvests in node negative CRC confer a

worse prognosis [9, 10, 12, 15, 16, 19, 21-24, 38, 51]. The reasons for this improvement could relate to stage migration, a more radical lymphadenectomy or lymph node hypertrophy, secondary to the patients own immune system fighting disease, making nodal identification easier. These reasons and the results of these previous studies have been discussed in detail in the introduction section of this thesis.

The data presented for Dukes' stage B patients also imply that the current twelve node national guidance [26-28] for lymph node retrieval may be too low, suggesting that at least fourteen nodes need to be harvested to more confidently assign a patient a node negative status. However, the finding that there was a statistically non-significant survival benefit in Dukes' stage B patients beyond a split of fourteen nodes could represent a type II statistical error. This result endorses the previous recommendations of Goldstein et al. [9] and Cserni et al. [13] that as many nodes as possible should be evaluated after CRC resection. The current NICE guidance of 12 nodes for lymph node retrieval [26] was published in 2004. Data presented in chapter two of this thesis reported that prior to the NICE guidance average national performance was less than the twelve node recommendation, since the guidance was issued, performance has improved. The results presented in this chapter advocate that the 12 node guidance should now be revised to a higher level. The worse survival in node negative patients at lower lymph node harvests also supports the opinion of some that adjuvant chemotherapy should be offered to node negative patients with a harvest of less than twelve nodes[144-147].

Survival following separating the Dukes' C (node positive) cohort according to nodal harvest, found that lower harvests were associated with a survival disadvantage. Below a level of <9 / ≥9 nodes there was a survival difference but above this level there was no difference. Previous studies have reported improved survival at higher levels of nodal harvests when cohorts of node positive patients have been analysed in a similar method to this chapter[10, 12, 13, 16, 19, 51]. However, these studies have observed differences in survival at higher separation points than the </ ≥ 9 node level found in the present study. There have also been several studies that have found that nodal yield does not influence survival in node positive cancer [14, 21, 22]. The worse survival at very low level of harvests in the current study could be explained by inadequate surgery, with an incomplete lymphadenectomy failing to clear a patient's disease. Alternatively it may be that tumour-host interaction has impacted on these results, with the inability of the host to mount a response leading to lower harvests because the nodes are not enlarged. This failure to mount a response would consequently negatively impact on the host's ability to resist the disease process, conferring worse survival [22, 111]. The less marked differences in survival according to lymph node harvest in Dukes' C cancers against Dukes' B imply that stage migration is responsible for the greater survival differences in node negative disease.

This chapter has found advancing age to be an independent predictor of survival following colorectal cancer resection in the whole study population and in separate analyses of Dukes' stage B and C disease. The finding that older age at diagnosis negatively impacts on survival is well reported [16-18, 153, 154]. In one large secondary analysis of pooled data from three chemotherapy randomised control trials, Sergeant et al. [155] found that patients over the age of 70 had a seven fold increased risk of non-cancer related death than patients aged less than 50. The mortality data provided by WICSU for analysis in this chapter included all causes of death, as opposed to cancer specific survival. It is therefore likely that the poorer prognosis observed with advancing age in this chapter is a reflection of the general increased risk of death in elderly patients from other causes.

Analysis of the whole study population found the number of positive nodes, advancing T and Dukes' stage, the number of nodes examined and emergency surgery independently predicted survival. The first three are pathological variables that represent more advanced disease. Their impact on survival is therefore unsurprising, with each of these variables well reported to negatively impact on survival from colorectal cancer [2, 8, 10, 16, 18, 19, 156]. The finding that lymph node harvest is a strong independent predictor of survival supports the importance of maximising nodal harvest after colorectal resection. Emergency surgery for colorectal cancer has also been widely recognised surgery to be a negative predictor of long term survival [25, 91, 153, 157].

In node negative cancer (Dukes' B) female sex was found to confer an independent survival benefit, although no difference in survival was observed in node positive (Dukes' C) disease. Improved female cancer specific and general survival has been frequently reported [158-161] following colorectal cancer. This may be due to the protective effects of oestrogens against microsatellite unstable cancers [159]. However, previous reports have found differences in survival in both node negative and node positive disease stages, the reasons for the variation from the norm observed in the current chapter are unknown.

In node positive disease (Dukes" C) the only independent predictors of survival were age and lymph node ratio (LNR). It has been well documented that higher numbers of lymph node metastases confer a worse survival [8, 15, 16, 19, 24, 162, 163], consequently this forms the basis of the nodal stage differentiation in the TNM staging system (see appendix 2), with "N1" having 1-3 nodes involved and "N2" having >4 nodes involved. Several recent studies have evaluated LNR as a prognostic indicator. Berger and colleagues [162] were the first to report on this, finding that LNR independently predicted survival of node positive colorectal cancer. Subsequently, Wang et al. [32] have analysed 24.477 node positive patients from the SEER database, splitting LNR into four sub-groups, they found after adjustment for age, race, number of positive lymph nodes and total number of lymph nodes harvested that LNR was an independent predictor of survival. De Ridder et al. [164], again using SEER data on over twenty six thousand patients, compared the prognostic value of splitting patients into two LNR groups (LNR1= <0.4 and

LNR 2 = >0.4) against the UICC pN1 and pN2 categories. They found that the prognostic separation was greater with the LNR staging system. They therefore concluded that it was a more prognostic indicator than pN1/2 staging system. In this chapter LNR was the only lymph node related variable that independently predicted survival in node positive disease, these data in conjunction with previous studies suggest that LNR should be adopted into future staging systems for node positive cancer.

There are some limitations with the data analysed in this chapter, which must be acknowledged. The data was submitted to CANISC and used to populate the WBCA report for this year [115]. In this audit year (2005-6) only twelve of the thirteen MDTs that treat bowel cancer participated in the audit. Although this has reduced the population size of the study it is not believed that this will have influenced the results as the case mix treated by the non-submitting unit should not be different from the remainder of units analysed. Data submission in 2005-6 was voluntary, it is therefore possible that not all cases of colorectal cancer in Wales in that year have been analysed. However, case ascertainment to the audit against colorectal cancer registrations with WICSU for this period [115] showed that, including the unit that did not participate, 84% of patients treated for bowel cancer in Wales in 2005-6 were represented in this chapter. If the unit that did not participate is excluded from analysis, 92% of patients with bowel cancer diagnosed in 2005-6 and registered with the cancer registry were included in data analysed in this chapter. It is therefore unlikely that missing patients will have significantly influenced results.

Whilst a potential strength of the data is its prospective capture, there have been problems with data accuracy and the amount of missing variables reported to the WBCA. This is exemplified by the data accuracy within the audit field, "Clinico-pathological Dukes' stage". This field has been problematic for the WBCA with patients with liver or lung metastases miss-staged as Dukes' stages A-C, as observed in the 25 cases amended in this chapter. This error is believed to arise because non-clinical MDT co-ordinators may submit the data with little clinician involvement. If this is representative, it is possible that there may have been other errors in data submission, which may have impacted on the results presented. Another area of difficulty experienced by the WBCA has been the number of missing fields in the audit. This is supported by the results of this chapter that found 122 (12%) of patients having a resection had no Dukes' stage or lymph node harvest recorded and that only 44% of patients undergoing resection had their ASA score submitted. The poor quality of ASA returns may have impacted on the analyses of variables predicting survival. ASA score can be considered as a surrogate marker of medical co-morbidity [165], it was therefore a surprising result that it did not independently predict survival. Increasing ASA score was found on all uni-variate analyses to predict worse survival but was excluded by the multi-variate model in all cases. This may have lead the model to erroneously dismiss ASA as an independent predictor.

The data collected for the WBCA has a limited number of variables, it is therefore likely that there are other independent predictors of survival that

have not been examined in the survival analyses. This may be particularly pertinent for node negative patients who may have other poor prognostic features, such as extra-mural vascular invasion, poor primary tumour differentiation or serosal involvement that have been shown to negatively impact upon survival and consequently have been advocated as indications for adjuvant chemotherapy [27, 144, 146, 166-168]. Data on theses variables was not collected by the WBCA in the year studied in this chapter. In addition to these tumour related variables not collected by the WBCA, data on adjuvant chemotherapy use was also not collected, the use of which is likely to have impacted on survival and could have impacted upon the results presented.

3.10 Conclusions

This chapter has found that increasing nodal harvest in Dukes' B (node negative) colorectal cancer independently predicts survival. The results suggest that a harvest of at least fifteen nodes is required to confidently stage a patient as node negative. In light of this, revision of the national twelve node guidance for lymph node harvesting following colorectal cancer surgery to a higher harvest level is suggested. In Dukes' C (node positive) colorectal cancer, lymph node ratio independently predicted survival and should be considered in future staging systems. This may, in the future, allow tailored adjuvant treatment for those patients at highest risk of recurrent disease.

4.1 Overall Discussion and Recommendations

This thesis has studied lymph node harvest in colorectal cancer resection, the chapters within have focused on and the factors than influence lymph node retrieval, intra-unit comparative audit and the impact that audit against national guidelines has on national nodal harvests and finally the importance of lymph node harvest on survival and prediction of prognosis in patients with colorectal cancer.

4.2 Discussion of methodology used in this thesis

This thesis used data from unit and national databases, the findings exemplify the strengths and weaknesses of research performed in this way; in chapter one access to local patient records and hospital electronic pathological systems, at a unit level, allowed complete data capture and accuracy. However, the smaller sample size of patients studied may have caused the null hypothesis to be rejected in some calculations when a larger study population may have found a statistical difference, a type II error. The use of locally collected data in chapter one also allowed the study of individual surgeon and pathologist performance, which is not possible with national data as this is analysed on a unit rather than individual clinician basis. In chapters two and three, use of national databases has allowed large numbers of patients to be studied but missing data and inaccuracies in data submitted may have potentially weakened the findings of these chapters. Ideally it

would be possible to have complete data capture at a national level. Electronic central submission of pathology reports directly into CANISC, at the time of specimen reporting, is planned in Wales in the near future and this will hopefully culminate in complete data capture for future study.

4.3 Factors that influence lymph node retrieval

This thesis has found reporting pathologist, unit of operation, type of operation and more pathologically advanced tumours independently influence the number of nodes harvested. The impact of reporting pathologist on nodal yields raises questions about the use of lymph node harvest as a marker of surgical quality. Whist this thesis found no difference in harvests between surgeons, it must be acknowledged that the radicality of surgery will undoubtedly impact on nodal yields and similar study in different units may demonstrate this. Thus, lymph node harvesting as a marker of combined surgical and pathological quality, but not surgical quality in isolation, has merit and can be recommended by the results presented in this thesis.

In section A of chapter one of this thesis, surgery for colonic cancers was associated with higher lymph node harvests than after rectal resection, particularly if pre-operative neo-adjuvant radiotherapy was administered. These findings are in agreement with the majority of the published literature on the subject. National guidelines for harvest after colorectal resection do not make any allowance for tumour site, given the findings in this thesis and of

previous work; it is a recommendation of this thesis that future guidance of nodal harvest should make allowance for tumour site.

Ultimately, the nodal harvest for any one individual patient will be dependent on several factors; the performance of the surgeon and pathologist and variables that relate to the patient and their tumour biology. When auditing the performance of surgeon and the pathologist, the variability in patient related variables needs to be allowed for using methods of risk adjustment.

4.4 Audit

This thesis has used the ACPGBI lymph node harvesting model to perform risk adjusted comparative audit of unit, individual pathologist and surgeon performance. Risk adjustment is important for any comparative audit of surgical performance because of the impact case mix can have on results, for instance a colorectal surgeon specialising in locally advanced rectal cancer resection would be expected to perform a higher proportion of post long-course APER operations, which according to the ACPGBI lymph node harvesting model and most published data would be expected to confer a lower harvest. Risk adjustment using the ACPGBI model makes allowance for these differences in case mix. However, the data in this thesis suggests that ACPGBI model is currently calibrated too low and needs re-calibration to a higher level.

Data from the Welsh Bowel Cancer Audit (WBCA) in chapter two, demonstrated the power of national guidelines and national audit to improve unit performance. The WBCA reports outcomes at a unit rather individual clinician level. The results of 'in-house' audit presented in chapter one, suggest that all units should audit individual members of their MDT. This may be of particular benefit to the small number of units in Wales who are yet to comply with the national guidance for lymph node harvest. It is therefore a recommendation of this thesis that all units should perform 'in-house' risk adjusted audit of the lymph node harvest of individual surgeons and pathologists and continue their participation in national audits.

4.5 The importance of lymph node harvest and ratio on survival

This thesis found that the number of lymph nodes harvested in node negative colorectal cancer impacts on a patients chance of survival; patients staged as node negative following examination of less nodes (up to a level of 15 nodes) had a 10-15% survival disadvantage compared to their counterparts who were staged as node negative following examination of more nodes. This finding suggests that at least 15 nodes should be examined in patients staged as node negative in order to minimise the risk of under staging a patient's disease.

National agencies currently recommend that at least twelve nodes should be examined following colorectal resection. Chapter three of this thesis found a survival difference of 14 % (56% vs. 70%) in patients staged as node negative

following examination of <12 and ≥12 nodes. This finding provides further support for the above recommendation that targets for nodal harvest need to be raised. In a patient initially staged as node negative following examination of less than 12 nodes, it is recommended that re-examination of the submitted specimen to increase nodal yield is appropriate. If the harvest remains less than 12 nodes consideration should be given to offering the patient adjuvant chemotherapy, even in the absence of other poor prognostic features.

The survival differences according to lymph node ratio (LNR) reported in chapter three suggests and that LNR may be a more sensitive prognostic indicator than the current lymph nodal staging systems. It is therefore a recommendation of this thesis that LNR should be considered for inclusion in future staging systems for colorectal cancer. The poorer survival experienced by patients with higher LNR suggests that these patients should be targeted for more aggressive chemotherapy regimens.

4.6 Conclusions

This thesis has demonstrated the importance of lymph node harvest following surgical resection for colorectal cancer. It has confirmed that surgical, pathological and patient related variables impact on nodal harvest. In house unit audit of individual clinicians is important and national audit against national guidelines are a powerful tool to improve performance.

5.1 Recommendations for future work

- The exceptional lymph node harvests achieved by the pathologist with a special interest in rectal cancer specimen reporting in chapter one, section B is worthy of further study. Examination of the factors that influence nodal retrieval in 'their hands' would allow study without pathologist as a variable, on the assumption that nodal harvest has been optimised by this individuals performance.

- Ex-vivo sentinel node examination of colorectal cancer specimens appears to have promise and is worthy of further study. In particular, using this technique to ultra-stage the sentinel node/s with immunohistochemical or molecular techniques could upstage tumours currently assigned a node negative status.

- Further study of patients assigned a node negative stage following a low lymph node harvest could be performed, to calculate the impact that other poor prognostic features such as extra-mural vascular invasion, poor tumour differentiation, mucinous tumour type or serosal involvement have on survival. This data could then be used to produce a risk model that calculates the risk of disease recurrence based on the presence or absence of these variables. This would allow an informed decision to be made about the use of adjuvant chemotherapy in this setting, allowing for the risk / benefit ratio of this treatment.

Peer Reviewed Publications arising from this thesis

1. Evans MD, Barton K, Rees A, Stamatakis JD, Karandikar SS. **The impact of surgeon and pathologist on lymph node retrieval in colorectal cancer and its impact on survival of patients with Dukes' stage B disease.** Colorectal Disease 2008;10(2): 157-164

2. Evans MD, Robinson S, Badiani S, Langman G, Rees A, Stamatakis JD, Karandikar SS. **Same Surgeon – Different Centre Equals Different Lymph Node Harvest Following Colorectal Cancer Resection.** International Journal of Surgical Oncology 2011 doi:10.1155/2011/406517

National and International presentations to arising from this thesis

1. Evans MD, Smith JJ, Stamatakis JD. **Open Reporting in a National Audit of Lymph Node Harvest Against National Guidance Improves Performance.** Association of Coloproctology Great Britain & Ireland Annual Meeting 2010, Colorectal Disease 2010; 12 (Suppl 1): 8

2. Evans MD, Robinson S, Rees A, Langman G, Stamatakis JD, Karandikar SS. **Same Surgeon – Different Centre Equals Differing Lymph Node Harvest.** Association of Coloproctology Great Britain & Ireland Annual Meeting 2008. Colorectal Disease 2008; 10 (Suppl 1): 10, Welsh Surgical Society Abstract Volume 51, May 2008, American Society of Colon & Rectal Surgeons Meeting 2008. Diseases of the Colon and Rectum 2008; **51** (5): 753

3. Evans MD, Stamatakis JD, Smith JJ. **Number of specimen lymph nodes examined after resection for bowel cancer is not affected by finding a metastatic node.** European Association of Coloproctology 2007. Colorectal Disease 2007; **9** (Suppl 3): 36 and Society of Academic and Research Surgeons 2008. British Journal of Surgery 2008; 95: S4: 25

4. Evans MD, Rees A, Stamatakis JD, Karandikar SS. **Lymph Node Harvest Influences Survival in Dukes' Stage B Colorectal Cancer.** Association of Coloproctology of Great Britain and Ireland, Gateshead 2006. Colorectal Disease 2006; **8**: (Supp 2): 63-64

Appendix 1 - Modified Dukes' Classification used in this thesis[5]

Dukes' A: Tumour limited to the bowel wall, lymph nodes negative

Dukes' B: Tumour spread beyond the muscularis propria, lymph nodes negative

Dukes' C1: Lymph nodes positive by highest node spared

Dukes' C2: Highest lymph node involved

Dukes' D: Distant metastases

Appendix 2 UICC TNM Classification of colorectal tumours [3]

pT Primary tumour

pTX Primary tumour cannot be assessed
pT0 No evidence of primary tumour
pT1 Tumour invades submucosa
pT2 Tumour invades muscularis propria
pT3 Tumour invades through muscularis propria into subserosa or non-peritonealised pericolic or perirectal tissues
pT4 Tumour directly invades other organs (pT4a) and/or involves the visceral Peritoneum (pT4b)

pN Regional lymph nodes

pNX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in 1 to 3 regional lymph nodes
pN2 Metastasis in 4 or more regional lymph nodes

pN Distant metastasis

pMX Distant metastasis cannot be assessed
pM0 No distant metastasis
pM1 Distant metastasis

pX prefix denoted pathological stage.
ypX prefix denoted post neoadjuvant preoperative chemotherapy or radiotherapy

Appendix 3 – American Society of Anesthesiologists Scoring System

I - A normal healthy patient.

II - A patient with mild systemic disease.

III - A patient with severe systemic disease.

IV - A patient with severe systemic disease that is a constant threat to life.

V - A moribund patient who is not expected to survive without the operation.

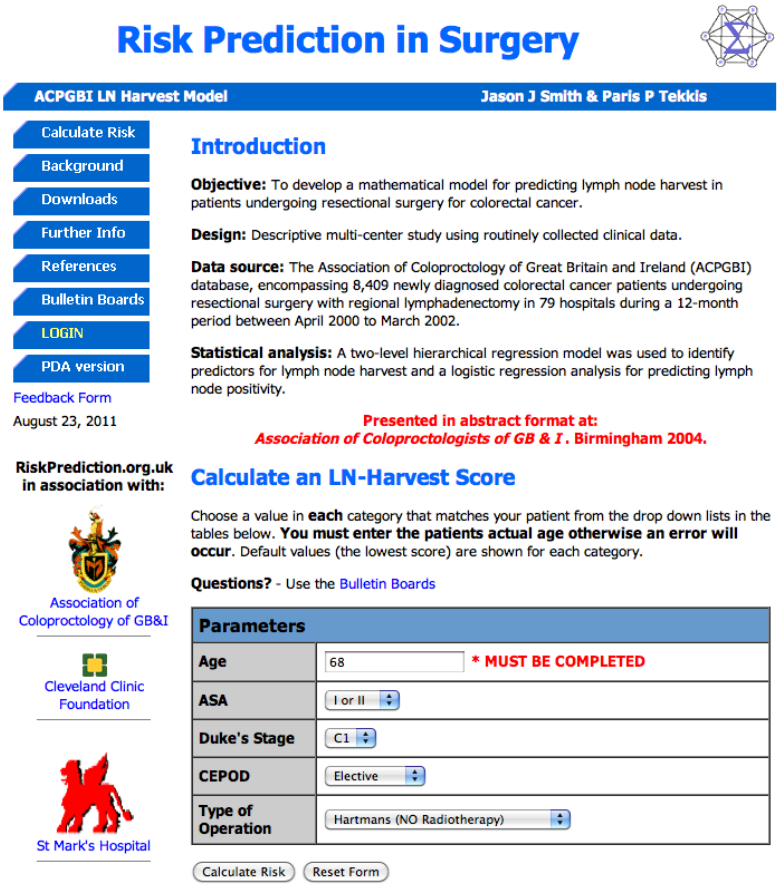
Appendix 4 – The ACPGBI lymph node harvest model[107]

Risk Factor		LN score
Age (years)		
	<20	-0.7
	21-30	-1.5
	31-40	-2.1
	41-50	-2.7
	51-60	-3.3
	61-70	-3.9
	71-80	-4.5
	81-90	-5.1
	>90	-5.7
ASA grade		
	I & II	0
	III	-0.6
	IV & V	-1.0
Operative urgency		
	Elective	0
	Urgent	-0.4
	Emergency	-1.3
Dukes' stage		
	A	0
	B	2.6
	C1	2.8
	C2	4.5
	D	2.5
Type of surgery		
	Right / Ext R hemicolectomy	0
	Subtotal colectomy	0.3
	Transverse colectomy	-4.5
	Left hemicolectomy	-1.8
	Sigmoid colectomy	-1.9
	Hartmann's procedure	
	without pre-op radiotherapy	-2.2
	with pre-op radiotherapy	-3.8
	Anterior resection	
	without pre-op radiotherapy	-1.0
	with pre-op radiotherapy	-2.6
	AP excision rectum	
	without pre-op radiotherapy	-1.7
	with pre-op radiotherapy	-5.4
Constant		**26.3**
ACPGBI lymph node score = 26.3 – sum lymph node score		

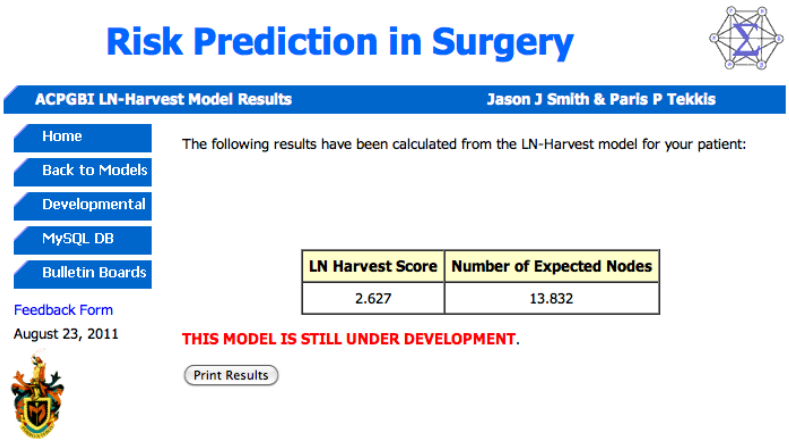
Total LN score	Predicted LN harvest
0	1
6.9	2
11.0	3
13.9	4
16.1	5
17.9	6
19.5	7
20.8	8
22.0	9
23.0	10
24.0	11
24.8	12
25.6	13
26.4	14
27.1	15
27.7	16
28.3	17
28.9	18
29.4	19
30.0	20
30.4	21
30.9	22

Appendix 5 – Demonstration of the use of the ACPGBI lymph node harvesting model to predict harvest

1. The model is found at www.riskprediction.org.uk, the variables for the patient are entered into the model, as shown.



2. The model calculates a predicted harvest for that individual patient



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