
Article:
Scott, N, West, NP orcid.org/0000-0002-0346-6709, Cairns, A et al. (1 more author) (2021) Is Medullary Carcinoma of the Colon Underdiagnosed ? An Audit of Poorly Differentiated Colorectal Carcinomas in a large NHS Teaching Hospital. Histopathology, 78 (7). pp. 963-969. ISSN 0309-0167

https://doi.org/10.1111/his.14310

Is Medullary Carcinoma of the Colon Underdiagnosed ? An Audit of Poorly Differentiated Colorectal Carcinomas in a large NHS Teaching Hospital.

Running title : Underdiagnosis of Colonic Medullary Carcinoma.

Dr N Scott[1], Dr NP West[2], Dr A Cairns[1], Dr O Rotimi[1].

[1]Department of Histopathology, Leeds Teaching Hospitals NHS Trust, Leeds, U.K.
[2]Pathology & Data Analytics, Leeds Institute of Medical Research at St James, University of Leeds, Leeds, U.K.

Correspondence to Dr N Scott, Department of Histopathology, Bexley wing, St James University Hospital, Leeds, U.K. email: nigel.scott3@nhs.net

Conflicts of interest : None of the authors has a conflict of interest to disclose.

Word Count : 2643

Abstract

Aims

Medullary carcinoma is an uncommon colorectal tumour which appears poorly differentiated histologically. Consequently it may be confused with poorly differentiated adenocarcinoma NOS. The principal aim of this study was to review a large series of poorly differentiated colorectal cancers resected at a large NHS Teaching Hospital to determine how often medullary carcinomas were misclassified . Secondary aims were to investigate how often neuroendocrine differentiation or metastatic tumours were considered in the differential diagnosis, and compare clinico-pathological features between medullary and poorly differentiated adenocarcinoma NOS.

Methods

Histology slides from 302 colorectal cancer resections originally reported as poorly differentiated adenocarcinoma were reviewed and cases fulfilling WHO criteria for medullary carcinoma identified. The original pathology report was examined for any mention of medullary phenotype, consideration of neuroendocrine differentiation or metastasis from another site. Clinico-pathological features were compared to poorly differentiated adenocarcinoma NOS.

Results

Only one third of medullary carcinomas were correctly identified between 1997 and 2018. The other two thirds were reported as poorly differentiated adenocarcinoma NOS. The possibility of an extracolonic origin or neuroendocrine carcinoma was considered in 21% and 27% of reports. Most medullary tumours exhibited mismatch repair deficiency, were located in ascending colon and caecum, and had a lower rate of vascular channel invasion and lymph node metastasis compared to poorly differentiated adenocarcinoma.

Conclusions

Medullary carcinoma of the colon is often mistaken for poorly differentiated adenocarcinoma NOS and occasionally for neuroendocrine or metastatic carcinoma. Greater familiarity with morphological criteria and use of mismatch repair protein staining should improve diagnosis.

Keywords : Colon, Medullary Carcinoma, Mismatch Repair Deficiency

Introduction

Over 80% of colorectal adenocarcinomas are of “no specific type” and reported as adenocarcinoma “NOS”. The remaining 20% contain a number of histological subtypes described in the 2010 WHO classification[1] and are included in most international Colorectal Cancer reporting datasets[2,3]. These include mucinous adenocarcinoma, signet ring cell carcinoma, medullary carcinoma, serrated adenocarcinoma, micropapillary carcinoma and cribriform comedo-type adenocarcinoma. While mucinous carcinomas are relatively common, the other types represent 5% or less of all tumours and may be unfamiliar to many pathologists without a special interest in gastro-intestinal pathology. It is estimated that medullary carcinoma represents 0.1% - 3 % of all colorectal cancers[4] and is defined by the WHO as a tumour with “sheets of malignant cells with vesicular nuclei, prominent nucleoli and abundant cytoplasm exhibiting prominent infiltration by intraepithelial lymphocytes”. In addition they almost invariably demonstrate microsatellite instability (MSI-H). In 2010 the WHO recommended that these tumours should not be graded in the same way as adenocarcinoma NOS since most, if not all, medullary carcinomas would be classified as poorly differentiated using conventional criteria. Despite this the majority of studies show medullary cancers have a much better prognosis stage for stage than poorly differentiated adenocarcinoma NOS[4].

Over the past 10 years we have seen a number of medullary carcinomas, both in biopsy and resection specimens, cause diagnostic difficulties. In particular, sheet-like growth and monotonous nuclear appearance often suggests neuroendocrine differentiation. In other cases the unusual morphology and aberrant immunohistochemical profile has led the reporting pathologist to consider a metastasis from outside the colorectum.

The principal aim of this study was to determine how often the diagnosis of medullary carcinoma is missed in routine reporting of colorectal cancer resection specimens in a large UK Teaching Hospital. **We also wished to review the histological and immunohistochemical features which may lead to diagnostic error.**

Materials & Methods

Colorectal carcinomas graded by the reporting pathologist as poorly differentiated or undifferentiated were identified from a prospectively maintained pathology database covering the period 1st January 1997 to 31st December 2018. Tumours arising in Familial Adenomatous Polyposis or Ulcerative Colitis and rectal cancers resected following short or long course radiotherapy were excluded. Grading and histological typing was performed by a specialist consultant GI pathologist or by a junior pathologist under supervision. Grading criteria were those described in the Royal College of Pathologists data set[2] and were largely based on extent and degree of gland formation as described in the WHO classification. Excluding neuroendocrine tumours and metastatic carcinoma , 311 out of 2933 (10.6 %) of cancers were

originally graded as poorly differentiated. 302 out of 311 cases (97.1 %) were retrieved from file and reviewed by NS. The slides for 9 cases could not be traced. Four or more tumour blocks were reviewed from 31 out of 33 cases reclassified as medullary (range 1 to 12). Medullary carcinoma was diagnosed using the WHO criteria (see above). Since it is widely recognised that these tumours do not always have a pure medullary morphology, in line with previous publications an arbitrary lower threshold of > 70% solid component was used for diagnosis and the percentage of other gland forming elements (0% - 30%) estimated. The original report was reviewed with particular attention to whether a medullary phenotype was recognised, the use of immunohistochemistry including mismatch repair protein staining, and the consideration of neuroendocrine differentiation or metastatic tumour. Demographic data, tumour site and tumour stage were obtained from the histopathology report and hospital patient information system (Patient Pathway Manager). All patient data was anonymised. **Clinico-pathological features were compared using Wilcoxons signed rank test for continuous variables ie. age and tumour size, and Fishers exact test for categorical variables.**

Results

311 tumours out of 2933 (10.6 %) were originally reported as poorly differentiated or undifferentiated. Out of the 302 cases retrieved from file, 87 were re-graded as well or moderately well differentiated using WHO criteria. The remaining 215 were confirmed to be poorly differentiated or undifferentiated (71.2 % of 302 reviewed cases and 7.3 % of all resected cancers).

33 out of 215 poorly differentiated carcinomas were classified as medullary carcinoma on review (15.3 %). This represents 1.1 % of all resections. Approximately one third of these were pure medullary carcinomas (32.1 %) and 67.9 % had a non-medullary component (see Figure 1).

Out of 33 cases, eleven (33.3 %) were recognised as having features of medullary carcinoma in the original report. The other two thirds were all described as poorly differentiated adenocarcinoma NOS with no qualification or mention of a medullary phenotype. Diagnosis of medullary type appeared to improve over time however. Between 1997 and 2004 none out of 3 tumours were recognised. One out of 4 tumours were correctly classified between 2005 and 2009, 3 out of 15 between 2010 and 2014 and in the last four years 7 out of 11 (63.6 %) tumours have been correctly attributed.

Possible metastasis from elsewhere or neuroendocrine differentiation were considered by the reporting pathologist in 21% and 27% of cases respectively. One out of 33 tumours was initially reported as metastatic breast carcinoma but subsequently confirmed to be a primary medullary carcinoma with no evidence clinically of a breast lesion. Immunohistochemistry for neuroendocrine markers chromogranin, synaptophysin or CD56 were performed and found to be negative in 9 cancers, while CDX2, CK20 and CK7 staining was undertaken in 8. All 8 tumours

stained for CK7 and 20 were negative for both markers while focal CDX2 positivity was detected in 2 out of 8.

Immunohistochemistry for the mismatch repair proteins had been performed in 22 out of 33 cases. Mismatch repair deficiency was identified in all 22 (100%). This involved a loss of hMLH1 staining in all cases.

Compared with poorly differentiated colorectal adenocarcinomas NOS, medullary carcinomas occurred more often in females and in an older age group (see Table 1). Over 90% of tumours were located proximal to the splenic flexure, predominantly in the ascending colon and caecum, and tended to be larger than adenocarcinoma NOS. Lymph node metastases and extramural venous invasion were reported less frequently (30.3% versus 75.1 % and 27.3 % versus 74 % respectively) but tumour perforation and R1 resections occurred at a similar rate in both types of carcinoma. Synchronous distant metastasis was present in 2.5 % of medullary carcinomas at presentation.

Discussion

Medullary carcinomas were first described in the colon by Jessurun et al in 1992[5] but are uncommon tumours , representing less than 3 % of all resected colorectal cancers. It is likely therefore that the unusual morphology of these lesions will be unfamiliar to many histopathologists and could lead to diagnostic uncertainty. The principal aim of this study was to determine how often medullary carcinomas are incorrectly diagnosed as poorly differentiated adenocarcinoma NOS in a large NHS Teaching Hospital with subspecialist reporting practise.

Out of 302 cases of poorly differentiated adenocarcinomas which were reviewed, 33 satisfied histological criteria for medullary carcinoma. Most of these (66.7 %) were originally reported as poorly differentiated adenocarcinoma NOS.

On account of their solid architecture, lack of mucin production and monotonous cytological features, medullary carcinomas without any glandular elements may easily be confused with neuroendocrine tumours and carcinomas. In our study the reporting pathologist ordered neuroendocrine immunohistochemical markers in 27 % of cases to specifically exclude neuroendocrine differentiation. Although a proportion of otherwise typical colorectal adenocarcinomas show focal positivity for neuroendocrine markers, no staining was seen in any of the medullary tumours.

Conversely the presence of more conventional mucinous or adenocarcinomatous components in 68% of cases, albeit representing < 30% of the tumour volume, often led the reporting pathologist to ignore the medullary phenotype altogether and classify the tumour as poorly differentiated adenocarcinoma NOS. Since most poorly differentiated adenocarcinomas behave much more aggressively than medullary

carcinoma this could potentially lead to overtreatment, particularly if mismatch repair or MSI testing is not performed.

In 21 % of reports the possibility of a metastasis to the colon was raised, and in one case this was the preferred diagnosis prior to MDT review. Errors in recognising medullary carcinomas as primary colorectal tumours are not helped by the atypical immunohistochemical profile often shown by these lesions. As shown in our study, medullary carcinomas are often CK20 and CDX2 negative. Previous authors describe CDX2 staining as focal, weak or absent in 81% - 87% of tumours[,6,7,8]. In the same studies CK20 was positive in only 25% - 44 % of cancers. Correct identification of medullary carcinoma is facilitated by staining for the mismatch repair proteins which reveals mismatch repair deficiency in most cases, while Calretinin and SATB2 are expressed in 73 % and 89% of tumours respectively[7,8]. Conversely medullary carcinoma often shows loss of expression of the tumour suppressor gene ARID1A[9] .

In contrast to medullary carcinoma, poorly differentiated adenocarcinomas are often CK20 and CDX2 positive. The large cell type of neuroendocrine carcinoma, which may resemble undifferentiated or medullary carcinoma of the colon, by definition shows significant immunopositivity for at least two out of three neuroendocrine markers synaptophysin, chromogranin and CD56. Table 2 highlights the main clinical and histological features distinguishing the three types of cancer.

Earlier studies have shown a strong association between the medullary phenotype and high level microsatellite instability (MSI-H). In the series reported by Ruschoff et al, Lanza et al and Knox et al , evidence of MSI or mismatch repair deficiency was found in 80% to 100% of all medullary tumours, while in reports of MSI tumour cohorts, medullary morphology is described in between 9% and 14% of cases[10,11,12,13,14]. This prevalence is in line with our own experience. Routine mismatch repair protein immunohistochemistry has been performed on all colorectal cancer biopsies and resections in our unit since May 2017 following the publication of NICE diagnostic guidance for Lynch Syndrome screening[15]. In a consecutive series of 81 cases, medullary morphology was found in 15% of all mismatch repair deficient tumours and 17% of those showing loss of expression of hMLH1 (unpublished observations).

The clinico-pathological features of medullary carcinomas are distinct from other colorectal carcinomas. Compared with adenocarcinoma NOS they occur in an older (predominantly female) population, are mainly right sided, show lower levels of vascular invasion and lymph node metastasis, and rarely present clinically as stage IV disease[4,11,12,15,16]. This was also evident in our series where 94 % were located proximal to the splenic flexure, lymph node metastasis was present in only 30% of cases and vascular invasion in 27%. Most studies suggest however, that despite their size and grade, prognosis is good[11,12,13,16].

While many of these features, including predisposition to occur in the proximal colon and infrequent lymph node metastasis, are common to all MSI positive tumours, recent studies have highlighted a number of potentially important differences in this genetically defined group. Tumours with mismatch repair deficiency are

morphologically heterogenous. In addition to the medullary pattern, there is also an increased proportion of mucinous carcinomas, signet ring cell carcinomas and tumours with more than one histological pattern. Compared to other types of MSI-H cancer, medullary carcinomas are more likely to express PD-L1, contain larger numbers of CD8 positive tumour infiltrating lymphocytes (TILs), and develop more mononucleotide frameshift mutations than MSI-H adenocarcinomas NOS[17,18,19]. These and other findings suggest that medullary carcinomas occupy a distinct immunoregulatory microenvironment with potential implications for prognosis and targeted immuno-therapies.

It is also likely that the mutation profile of medullary carcinomas is distinct from that of other mismatch repair deficient tumours. For example while loss of expression of ARID1A, a protein involved in chromatin remodelling, is seen in 24% of all MMR deficient tumours, the rates in medullary and non-medullary MSI positive tumours are 62% and 13% respectively. By comparison in microsatellite stable cancers the rate is only 4%[9]. Interestingly previous studies suggest most cases of loss of expression of ARID1A are due to inactivating mutations in a long mononucleotide repeat sequence found within the coding region of the gene[20].

Whereas most studies to date have analysed microsatellite unstable cancers as a single group and found reproducible differences in prognosis from microsatellite stable tumours, there are relatively few publications describing prognostic or predictive markers within the MSI-H cohort. Amongst microsatellite stable cancers tumour type and grade are well recognised prognostic factors. This is more controversial in the MSI-H cohort. In 2014 Rosty et al concluded that high grade tumours with MSI should be merged with MSI and MSS low grade tumours in a single low grade category on the basis of similar survival curves[21]. This was also recommended in the WHO 2010 classification of colorectal tumours whereas the new 5th edition published in 2019 is more circumspect and advises grading of certain types of MSI positive tumours e.g. mucinous carcinoma, using conventional criteria[1,22]. Recently in a series of 116 mismatch repair deficient carcinomas, Johncilla et al reported that high grade microsatellite unstable tumours (defined as < 50% gland formation, mucinous carcinoma or signet ring cell carcinoma) presented more often as stage III or IV disease (46% versus 23%) and experienced a higher rate of disease recurrence than low grade tumours[23]. Although numbers were small, the worst disease free survival was seen in MSI-H carcinomas with predominantly solid architecture, which in principle would contain most if not all medullary carcinomas.

Therefore while most reported series of medullary carcinoma suggest that clinical stage at presentation and survival are substantially better than microsatellite stable poorly differentiated adenocarcinoma NOS, it remains unclear whether prognosis is better, worse or equivalent to other microsatellite unstable tumours.

In conclusion between 1997 and 2018, medullary carcinoma of the colon was under diagnosed in 66 % of cases, and while identification has improved in recent years, a significant minority are still reported as poorly differentiated adenocarcinoma NOS. Whether this matters now that MSI testing or immunohistochemistry for mismatch

repair protein deficiency is recommended as routine for all colonic tumours is debatable, but we would argue that there are sufficient molecular and pathological differences between medullary and non-medullary MSI-H cancers to justify continued histological typing. It is important that histopathologists are familiar with this rare type of colonic adenocarcinoma, not least in view of frequent confusion caused by the unusual morphology raising the possibility of neuroendocrine differentiation or metastasis from elsewhere.

There are a number of limitations to our study. The denominator is all surgically resected colorectal carcinomas. Therefore advanced, metastatic tumours in which surgery was contraindicated and tumours occurring in elderly patients unfit for surgery are not represented in this series. Secondly we chose to review only cancers originally reported as undifferentiated or poorly differentiated as it seems likely that using a definition of medullary carcinoma in which > 70% of the tumour shows a solid growth pattern, this would capture the vast majority, if not all medullary tumours. Ideally however, we should have reviewed all cases. The diagnostic criteria for a medullary tumour is taken from the WHO description and we used a 70% cut-off as this is most commonly used by other authors, although it must be acknowledged that thresholds as low as 50% and as high as 100% have occasionally been employed. Only a single author (NS) reviewed the slides. This has the advantage of more uniform interpretation but we acknowledge that inter-observer variation exists in the diagnosis of medullary features and it is possible borderline cases may have been differently categorised by another pathologist[24]. It seems reassuring however that all cases in which MMR immunohistochemistry was performed showed MMR deficiency, including those where the original pathologist failed to recognise medullary morphology. A final limitation is the unavailability of MMR and Cytokeratin/CDX2 immunohistochemistry for all tumours, but the pattern of staining seen in those tested is consistent with previous series.

Acknowledgements : We would like to thank Mr M Todd for assistance with photomicrography and preparation of images. There are no funding sources to declare.

All authors were involved in the design and analysis of the study. Histology review and manuscript preparation was performed by Dr N Scott.

References.

1. WHO Classification of Tumours of the Digestive System 4th Edition. Ed. Bosman FT, Carneiro F, Hruban RH, Theise ND. IARC 2010.

2. Loughrey MB, Quirke PQ, Shepherd NA. Dataset for histopathological reporting of colorectal cancer. September 2018. Royal College of Pathologists.

3. College of American Pathologists. 2020. https://documents.cap.org/protocols/cp-gilower-colonrectum-resection-20-4100.pdf

4. Pyo J, Sohn J, Kang G. Medullary carcinoma in the colorectum: a systematic review and meta-analysis. Hum Pathol. 2016 ; 53 ; 91-96.

5. Jessurun J, Romero-Guadarrama M, Manivel JC. Cecal poorly differentiated adenocarcinoma, medullary type. Mod Pathol. 1992 ; 5 ; 43A.

6. Hinoi T, Tani M, Lucas PC et al. Loss of CDX2 Expression and Microsatellite Instability are prominent features of Large Cell Minimally Differentiated Carcinomas of the Colon. Am J Pathol. 2001 ; 159; 2239-2248.

7. Winn B, Tavares R, Fanion J et al. Differentiating the undifferentiated: immunohistochemical profile of medullary carcinoma of the colon with an emphasis on intestinal differentiation. Hum Pathol. 2009 ; 40 ; 398-404.

8. Lin F, Shi J, Zhu S et al. Cadherin 17 and SATB2 are Sensitive and Specific Immunomarkers for Medullary Carcinoma of the Large Intestine. Arch Pathol Lab Med. 2014; 138; 1015-1026.

9. Ye J, Zhou Y, Weiser MR et al. Immunohistochemical detection of ARID1A in colorectal carcinoma : loss of staining is associated with sporadic microsatellite unstable tumors with medullary histology and high TNM stage. Hum Pathol. 2014; 45; 2430-2436.

10. Ruschoff J, Dietmaier W, Luttges J et al. Poorly Differentiated Colonic Adenocarcinoma, Medullary Type. Clinical, Phenotypic and Molecular Characteristics. Am J Pathol. 1997 ; 150 ; 1815-1825.

11. Lanza G, Gafa R, Matteuzzi M, Santini A. Medullary type poorly differentiated adenocarcinoma of the large bowel : a distinct clinicopathologic entity characterised by microsatellite instability and improved survival. J Clin Oncol. 1999 ; 17 ; 2429-2438.

12. Knox RD, Luey N, Sioson L et al. Medullary Colorectal Carcinoma Revisited : A Clinical and Pathological Study of 102 Cases. Ann Surg Oncol. 2015 ; 22 ; 2988-2996.

13. Jass JR. HNPCC and sporadic MSI-H colorectal cancer: a review of the morphological similarities and differences. Fam Cancer. 2004; 3; 93-2004.

14. Alexander J, Watanabe T, Wu T, Rashid A, Li S, Hamilton SR. Histopathological Identification of Colon Cancer with Microsatellite Instability. Am J Pathol. 2001; 158; 527-535.

15. NICE guidelines. Molecular Testing strategies for Lynch Syndrome in people with colorectal cancer. 2017. https://www.nice.org.uk/guidance/dg27

16. Thirunavukarasu P, Sathaiah M, Singla S et al. Medullary carcinoma of the large intestine : a population based analysis. Int J Oncol. 2010 ; 37 ; 901-907.

17. Friedman K, Brodsky AS, Lu S et al. Medullary carcinoma of the colon : a distinct morphology reveals a distinctive immunoregulatory microenvironment. Mod Pathol. 2016 ; 29 ; 528-541.

18. Rosenbaum MW, Bledsoe JR, Morales-Oyarvide V, Huynh TG, Mino-Kenudson M. PD-L1 expression in colorectal cancer is associated with microsatellite instability, BRAF mutation, medullary morphology and cytotoxic tumor-infiltrating lymphocytes. Mod Pathol. 2016 ; 29 ; 1104-1112.

19. Shia J, Schultz N, Kuk D et al. Morphological characterization of colorectal cancers in The Cancer Genome Atlas reveals distinct morphology-molecular associations: clinical and biological implications. Mod Pathol. 2017; 30; 599-609.

20. Jones S, Li M, Parsons D et al. Somatic mutations in the Chromatin Remodeling Gene ARID1A occur in several tumor types. Hum Mutat. 2012 ; 33; 100-103.

21. Rosty C, Williamson EJ, Clendenning M et al. Should the grading of colorectal adenocarcinoma include microsatellite instability status ? Hum Pathol. 2014 ; 45 ; 2077-2084.

22. WHO classification of Tumours 5th Edition : Digestive System Tumours. IARC 2019.

23. Johncilla M, Chen Z, Sweeney J, Yantiss RK. Tumor Grade is Prognostically Relevant Among Mismatch Repair Deficient Colorectal Carcinomas. Am J Surg Pathol. 2018 ; 42 ; 1686-1692.

24. Lee LH, Yantiss RK, Sadot E et al. Diagnosing colorectal medullary carcinoma: interobserver variability and clinicopathological implications. Hum Pathol. 2017 ; 62 ; 74-82.

	Medullary Carcinoma	Poorly Differentiated Adenocarcinoma NOS	P value
Age (median)	**79**	**73**	**P 0.04**
Gender (F : M)	**25 : 8 (76 % female)**	**80 : 100 (44 % female)**	**p 0.001**
Size : median (range)	**60 mm (20 – 140 mm)**	**45 mm (13 – 145 mm)**	**P 0.0009**
Right sided	**31/33 (93.9 %)**	**104/175 (59.4 %)**	**p 0.05**
Left sided	**2/33 (6.1 %)**	**71/175 (40.6 %)**	
Mucinous histology	**0/33 (0 %)**	**37/181 (20.4 %)**	**p 0.002**
Tumour perforation	**3/33 (9.1 %)**	**17/173 (9.8 %)**	**p NS**
EMVI	**9/33 (27.3 %)**	**134/181 (74 %)**	**P 0.00001**
pT1 or pT2	**2/33 (6.1 %)**	**10/181 (5.5 %)**	**p NS[1]**
pT3	**18/33 (54.5 %)**	**65/181 (35.9 %)**	
pT4	**13/33 (39.4 %)**	**106/181 (58.6 %)**	**p NS[2]**
pN0	**23/33 (69.7 %)**	**45/181 (24.9 %)**	**p 0.00001[3]**
pN1	**4/33 (12.1 %)**	**41/181 (22.7 %)**	
pN2	**6/33 (18.2 %)**	**95/181 (52.5 %)**	
pR1 or pR2	**5/33 (9.1 %)**	**17/173 (9.8 %)**	**p NS**

Table 1. Clinico-pathological features of medullary and poorly differentiated adenocarcinoma NOS. N.B. In a minority of cases clinical/pathological data was missing from the report.

1 = pT1&2 versus pT3 & 4 ; 2 = pT1,2&3 versus pT4 ; 3 = pN0 versus pN1 & pN2.

	Medullary carcinoma	Poorly diffn adenocarcinoma	Large Cell Neuroendocrine carcinoma
Age	**elderly**	**elderly**	**elderly**
Site	**usually right colon**	**often right colon**	**often right colon**
M:F	**F > M**	**M > F**	**M > F**
T stage	**commonly T3/4**	**commonly T3/4**	**Commonly T3/4**
N stage	**< 40% N1/2**	**> 60% N1/2**	**> 60% N1/2**
M stage	**rarely M1**	**commonly M1**	**commonly M1**
Growth pattern	**Mainly solid, sheet-like or trabecular. May be focal gland formation."syncitial"**	**Irregular, poorly formed glands mixed with more solid areas.**	**Solid or trabecular. May be rosettes. Peripheral palisading.**
Cell morphology	**Uniform medium to large cells with eosinophilic cytoplasm. Poorly defined cell borders. Regular ovoid nuclei with nucleoli.**	**Pleomorphic cells varying in size and shape. Pleomorphic nuclei with nucleoli.**	**Uniform medium to large cells with eosinophilic cytoplasm. Regular round and ovoid nuclei +/- nucleoli.**
mucin	**rare***	**may be present**	**absent**
TILs	**common**	**rare**	**rare**
CK20	**< 50% positive**	**>70% positive**	**< 10% positive**
CDX2	**< 30 % positive**	**>70% positive**	**>70% positive**
Chromogranin & Synaptophysin	**negative**	**occasional cells only (< 10%)**	**positive**
Mismatch Repair proteins	**Abnormal > 90%**	**Abnormal 20 - 30%**	**Abnormal < 20%**

Table 2. Comparison of clinical and pathological features of medullary carcinoma, poorly differentiated adenocarcinoma and large cell neuroendocrine carcinoma.

* mucin absent in areas with medullary morphology but may be present in non-medullary areas of heterogenous tumours.

Figure 1a. Medullary Carcinoma. Note solid architecture and prominent tumour infiltrating lymphocytes (H&E x400).

Figure 1b. Typical solid Medullary Carcinoma on the right with Non-Medullary Mucinous component on the left (H&E x 200).

Figure 1c. Medullary carcinoma. Note regular ovoid nuclei and TILs (H&E x400).

Figure 1d. Poorly differentiated adenocarcinoma NOS. Note nuclear pleomorphism and small, irregular gland formation (H&E x400).