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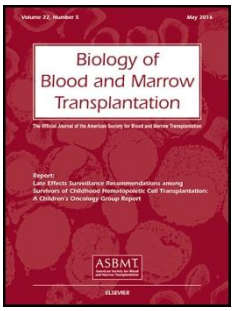

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"Diagnostic utility of endoscopy and biopsy in suspected acute gastrointestinal graft versus host disease (GI-GVHD) following haematopoietic progenitor cell transplantation (HPCT)."

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Highlights:

- Routine performance of upper endoscopy does not significantly increase diagnostic yield for GI-GVHD.
- Diarrhoea and advanced age are the only predictors for identifying histological GVHD in patients suspected of having GI-GVHD.
- Of the patients who are ultimately treated for GI-GVHD, only 74% have GVHD confirmed on biopsy, thus highlighting a need for improved diagnostic techniques.

ABSTRACT

Background / Aim:

Acute gastrointestinal graft versus host disease (GI-GVHD) following haematopoietic progenitor cell transplantation (HPCT) is a common and life-threatening complication. Endoscopic biopsy of the gastrointestinal tract is required for diagnosis. However, clear evidence to optimise this diagnostic approach is lacking, leading to variation in diagnostic sensitivity between institutions. We aimed to assess the clinical, endoscopic and histological findings of endoscopies performed for suspected acute GI-GVHD at our institution to better define the optimal use of this strategy.

Methods:

We performed a retrospective cohort study of adults who had undergone endoscopy for suspected acute GI-GVHD within 180 days following allogeneic HPCT for haematological malignancy between 2011-2016. Details included: symptoms at time of referral for endoscopy, type of procedure performed, macroscopic findings on endoscopy, and histological findings following gut biopsy. Correlation was made with clinical GVHD severity scores. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated and compared for each procedure. Predictors of histological GVHD and overall survival were also compared.

Results:

Of the 123 patients included, acute GI-GVHD occurred in 59 (48%). Lower endoscopy demonstrated greater sensitivity than upper endoscopy (50% *vs.* 39%). Single upper endoscopy for upper symptoms alone had the lowest yield of GI-GVHD (14%). Combination upper and lower endoscopy demonstrated strong histological concordance between upper and lower procedures. The addition of upper endoscopy to lower endoscopy only identified an extra 2 (4%) cases of GVHD. Advanced age and the presence of lower GIT symptoms were the only pre-endoscopy predictors of histological GVHD on multivariate analysis. Patients with isolated upper histological GVHD showed similar survival to patients with negative biopsies. Endoscopy and biopsy only identified 74% of those ultimately requiring treatment for acute GI-GVHD.

Conclusion:

Acute GI-GVHD remains a clinical diagnosis supported by available histological evidence. Isolated upper gastrointestinal GVHD is rare, and in the absence of lower GIT symptoms routine upper endoscopy does not significantly improve diagnostic yield for histological GVHD. Overall, endoscopy and biopsy underdiagnoses 26% of clinical GI-GVHD, highlighting a need for research into novel diagnostic strategies.

Keywords: GVHD; Endoscopy; HPCT; gastrointestinal

INTRODUCTION

Acute gastrointestinal graft versus host disease (GI-GVHD) is a common and potentially life-threatening early complication following haematopoietic progenitor cell transplantation (HPCT). GI-GVHD is characterised by donor T-cell mediated invasion and inflammation of the gastrointestinal tract (1, 2), and the cardinal histological feature is cellular apoptosis. Symptoms include profuse diarrhoea, abdominal pain, and bleeding or perforation in severe cases. Clinical diagnosis of GI-GVHD is often confounded by other conditions that produce similar symptoms; such as gastrointestinal infection from clostridium difficile or cytomegalovirus (CMV) reactivation, or direct gut toxicity from conditioning chemotherapy.

The accepted standard diagnostic method for GI-GVHD is endoscopic visualisation and biopsy of the gastrointestinal tract (GIT), however the utility of this approach is influenced by numerous variables. Patchy GIT distribution of GI-GVHD may cause sampling error, as affected areas (such as the small bowel or proximal colon) may be inaccessible for biopsy. Performing biopsies only in macroscopically abnormal tissue may miss GI-GVHD, as up to 60% of macroscopically normal gut demonstrates histological GVHD (3, 4). Histological features of GI-GVHD can be non-specific, are highly reliant on the exclusion of confounding diagnoses such as CMV reactivation, and histological grade not appear to correlate with clinical severity (3, 5, 6). Less well evaluated are the potential confounding influences of clinical findings and management upon diagnostic yield of endoscopy and biopsy. The severity (Glucksberg stage and grade) and location (upper or lower GIT) of symptoms likely influences the decision to perform endoscopy, and the choice of procedures performed (upper or lower endoscopy, or both).

Prospective studies (3, 4) of endoscopy in symptomatic patients included routine biopsy of GIT sites that were not macroscopically suspected of being involved by GI-GVHD, in addition to macroscopically abnormal lesions. These data suggest that when using this approach GI-GVHD can be histologically identified in 60-88% of patients, with greater yield in lower endoscopy (80-90%) compared with upper endoscopy (60-70%), and greatest yield in combination upper and lower endoscopy (>90%). Retrospective data, assessing endoscopy performed only in the presence of clinical suspicion, demonstrate diagnostic yields in upper (27-84%) and lower endoscopy (50-80%) generally less than those seen in the prospective trials (7-10). Whether the greater diagnostic yield of histological GVHD identified in prospective trials correlates with improved response to anti-GVHD treatment, or survival, remains unknown.

For these reasons, practice regarding initiation of endoscopy (at onset of early stage versus moderate-severe stage clinical GVHD, or at defined time points in asymptomatic patients), choice of procedures (single versus combined upper and lower endoscopy) and biopsy sites (limited versus extensive) differs between

transplant institutions. Against this background, we aimed to retrospectively assess all patients treated in our institution who underwent endoscopic biopsy for suspected acute GI-GVHD post-HPCT, and compare the clinical, endoscopic and histological findings to evaluate the performance of this diagnostic strategy.

MATERIALS AND METHODS

Population details

Consecutive adult patients who underwent matched sibling or volunteer unrelated allogeneic HPCT for haematological malignancy, or donor lymphocyte reinfusion (DLI) for post-HPCT relapse, between January 2011 and December 2016 were identified from an institutional database. All patients who underwent upper and/or lower endoscopy during the first 180 days post-HPCT (D+180) were then identified from a separate database detailing all endoscopic procedures performed during this period.

Data pertaining to only the first endoscopic procedure prior to D+180 were included for assessment. Details included: clinical findings (symptoms) and severity at the time of referral for endoscopy, type of procedure performed, macroscopic findings on endoscopy, and histological findings following gut biopsy. Correlation was made with the incidence of a final clinical diagnosis of GI-GVHD, defined if the treating physician had documented GI-GVHD in the medical record as the final clinical diagnosis, *and* if the episode resulted in the patient being treated for acute GI-GVHD using a minimum of prednisone 1-2mg/kg/day.

HPCT details

All patients underwent T-cell replete HPCT. Myeloablative conditioning (MAC) regimens included cyclophosphamide 60mg/kg/day D-5 and D-4, *plus* total body irradiation 2Gy bd D-3 to D-1 (Cy/TBI). Reduced intensity conditioning (RIC) regimens included: fludarabine 25mg/m^2 D-7 to D-3 *plus* melphalan 120mg/m^2 D-2 (Flu-Mel). Non-myeloablative conditioning (NMAC) regimens included fludarabine 25mg/m^2 D-8 to D-4 *plus* cyclophosphamide 60mg/kg/day D-3 and D-2 (Flu-Cy) and fludarabine 30mg/m2 D-4 to D-2 *plus* total body irradiation 2Gy D-1 (Flu-TBI). GVHD prophylaxis for MAC and RIC transplants consisted of intravenous cyclosporine A (CsA), *plus* D+1, +3, +6 and +11 methotrexate. GVHD prophylaxis for NMAC transplants included oral CsA *plus* mycophenolate mofetil (MMF).

Definitions

All patients undertaking endoscopy evaluation were clinically suspected to have GI-GVHD. Symptoms leading to referral for endoscopy were defined as either upper (any / all of nausea, vomiting, anorexia), lower (any / all of diarrhoea, abdominal pain / cramps, ileus, perforation, fresh bleeding per rectum), or both. The clinical severity of suspected GVHD was defined as per modified Glucksberg criteria (5).

Endoscopic procedures were defined as either upper (upper endoscopy, gastroscopy, oesophagoduodenoscopy), lower (rectosigmoidoscopy, flexible

sigmoidoscopy, colonoscopy) or combined (both upper and lower endoscopy). Capsule endoscopy was not included. The incidence of concurrent skin or liver GVHD occurring within 4 weeks prior to or following the endoscopy was recorded. The incidence of patients receiving prednisone at a dose of 0.5mg/kg or greater on the day of endoscopy was also recorded, as was the rationale for commencing prednisone.

The decision regarding the choice of either upper, lower or combination endoscopies (including decision-making regarding rectosigimoidoscopy versus full colonoscopy for lower endoscopic procedures) was made by consultation between referring haematologist and performing gastroenterologist.

Macroscopic findings were defined as either suspicious for GVHD (any / all of ulceration, oedema, inflammation, bleeding) or not suspicious for GVHD (normal or polyps). Biopsy sites were chosen during the procedure based on the clinical judgement of the performing gastroenterologist.

Histological findings were defined as positive for GVHD if either a) the biopsy had been reported as GVHD, or b) the biopsy was reported as being suspicious of GVHD and CMV co-infection had been excluded. The histological grade of GVHD (Grade I-IV), where reported, was included as per previously defined criteria (3, 6). The final clinical diagnosis was defined as per the documentation in the medical record.

Statistical analysis

The incidence of histological GVHD was used to define the diagnostic sensitivity of individual procedures. Fisher's exact test was used for assessment of 2x2 contingency tables for categorical variables. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each contingency table. A stepwise logistic regression model was used for multivariate analysis of co-variables that were significantly associated with histological GVHD. Survival analysis was calculated using the Kaplan-Meier method. Statistical analysis was performed using Prism 7 (GraphPad, California USA) and Stata 12 (Statacorp, Texas USA).

RESULTS

Population characteristics

Of a total 551 HPCT procedures performed during the period, 123 patients (22%) underwent endoscopic evaluation for clinically suspected GVHD prior to D+180 post-HPCT and were included for analysis. Baseline characteristics are summarised in Table 1.

Clinical, endoscopic and histological findings

In the 123 patients who underwent endoscopic investigation prior to D+180 post HPCT, a total of 111 upper and 109 endoscopies were performed, at a median 43 days post HPCT or DLI (range 9-180 days). Details are summarised in Table 2. 79% of patients underwent combination endoscopy. All patients had at least one biopsy taken during their upper and / or lower endoscopies. At the time of endoscopy, 42 (34%) patients had been diagnosed with GVHD of skin and/or liver in the preceding 4 weeks, and 40 (33%) patients were still receiving prednisone at a minimum dose of 0.5mg/kg/day.

The most common clinical indication for endoscopy was concurrent upper and lower symptoms (n=62; 50%), with isolated lower symptoms alone (n=44; 36%) or upper symptoms alone less frequent (n=17; 14%). Single upper endoscopy was predominantly performed for isolated upper symptoms (71%), single lower endoscopy predominantly for isolated lower symptoms (75%), and combination endoscopy predominantly for combined symptoms (56%). In terms of symptom severity, the median Glucksberg clinical stage was 1 (range 0-4), with 17 (14%) patients classified as severe (Stage III-IV).

Macroscopic GVHD was reported in 74 (60%) of endoscopies overall, but at similarly lower rates for single upper or single lower procedures (43% *vs.* 44% respectively). In those who underwent combination endoscopy, only 23% had both upper and lower macroscopic GVHD.

Histological GVHD (Table 3) was identified in 59 patients, representing 48% of the study cohort and 11% of total HPCT recipients during this timeframe. Histological GVHD was more common in lower or combination endoscopy than in upper endoscopy (50%, 50% and 39% respectively). Sigmoid (48%) and rectum (45%) were the most commonly involved sites, compared to duodenum (38%) and stomach (27%); in all four patients who underwent full colonoscopy, proximal and distal colon were simultaneously involved. Notably, isolated upper histological GVHD was rare, identified in only 4% of all upper endoscopies (14% of single upper endoscopy), compared with simultaneous upper and lower histological GVHD (41% of combined endoscopies), or isolated lower histological GVHD (15% of all lower endoscopies).

A final clinical diagnosis of GI-GVHD was reached in 76 (62%) patients overall; the final clinical diagnosis in the remaining 47 patients was either CMV disease (5; 4%), *C.Difficile* gastroenteritis (5; 4%), or drug-related diarrhoea (37; 30%). Of the 76 GI-GVHD patients, 56 (74%) had histologically confirmed GVHD on endoscopic biopsy. All 76 patients were treated for GI-GVHD based upon their gastrointestinal symptoms, using either prednisone 1mg/kg or equivalent or greater. The presence of co-existing skin and/or liver GVHD, occurring within four weeks prior to or following endoscopy, was similar in patients with or without histological GI-GVHD (50% *vs.* 45%; p=0.79).

Of the 123 patients, 36 (29%) underwent a repeat endoscopic biopsy within 30 days following their original endoscopy. Histological GVHD was identified in 19 (53%) of those patients. Repeat endoscopy occurred more frequently in those who had been treated for a final clinical diagnosis of GI-GVHD compared to those with alternative final clinical diagnoses (42% *vs.* 9%; p=0.0001), however histological GVHD in the repeat biopsies was reported at a similar frequency between these two groups (50% *vs.* 75%; p=0.60).

Statistical analysis

Statistical analysis was undertaken to identify variables statistically associated with histological GVHD, and variables that improved the diagnostic sensitivity (48%), specificity, PPV and NPV of endoscopic procedures.

Pre-endoscopy, lower gastrointestinal symptoms showed greater sensitivity than upper symptoms (97% *vs.* 63%) and improved NPV (88% *vs.* 49%). In those patients who had upper symptoms at the time of upper endoscopy, almost all (94%) had co-existing lower symptoms; no histological GVHD was identified in the remaining 6% without co-existing lower symptoms. Advanced clinical stage (Glucksberg III-IV) demonstrated poor sensitivity (25-28%) but high specificity (96%) and PPV (80-85%) for histological GVHD in all endoscopies. Sensitivity was not significantly affected by prednisone usage prior to endoscopy (53%) or recent skin / liver GVHD (49%), however both showed high PPV for a final clinical diagnosis of GI-GVHD (100% and 93% respectively).

During endoscopy, macroscopic GIT abnormalities showed a high sensitivity (80%) for histological GVHD across all endoscopies. However, macroscopic findings in upper endoscopy were less predictive of histological GVHD than those in lower or combination endoscopy (sensitivity 53%, 71% and 79% respectively). In combination endoscopy, there was a strong correlation between histological findings at upper versus lower biopsy sites: 95% of patients with upper GVHD had co-existing lower GVHD identified, and 85% of patients with lower GVHD had co-existing upper GVHD identified.

Histological grade correlated poorly with advanced clinical stage grade in proven GVHD, with PPV of advanced findings in both categories only 47%. However, correlation between early stage / low grade GVHD appeared stronger, with specificity 80% and NPV 73%.

A clinical diagnosis of GVHD demonstrated PPV 74% and NPV 94% for histological GVHD.

Multivariate analysis

Logistic regression analysis was performed to identify pre-endoscopy predictors of histological GVHD (Table 4). The only factors remaining significant on multivariate analysis were lower symptoms (diarrhoea OR 8.13, p=0.01; cramps OR 2.59, p=0.03) and age at HPCT (OR 1.06, p<0.001). Notably, the use of prednisone pre-endoscopy was not associated with a subsequent diagnosis of histological GVHD.

Survival

At a median 24 months' follow-up, overall survival (OS) for the entire cohort is 56.9%, with median OS 3.6 years for the entire cohort.

Patients with positive clinical and histological diagnosis of GI-GVHD showed significantly inferior survival compared to patients with clinical and histological diagnoses negative for GI-GVHD (1-yr OS 48.2% *vs.* 88.6%; p=0.001, Hazard Ratio [HR] 0.71 [0.58-0.87]) (Figure 1). Although patients with discordant final clinical and histological diagnoses showed 1-yr OS of 65.0-66.7%, their OS was still significantly inferior to those with negative clinical and histological diagnoses.

Figure 2 depicts survival analysis based upon the site of histological GVHD involvement. Notably, patients with isolated histological upper GVHD had similar OS to patients who had negative histology from all biopsy sites (1-yr OS 75.0% and 81.2% respectively), compared to inferior survival seen in patients with either isolated lower histological GVHD or combined upper and lower histological GVHD (1-yr OS 37.5% and 51.2% respectively; p=0.02, HR 0.81 [0.67-0.97]).

DISCUSSION

This study retrospectively compared the clinical, endoscopic and histological findings in post-HPCT patients to assess the performance of the current accepted diagnostic strategy for defining GI-GVHD. Results from our cohort suggest that histological GVHD is only present in 40-50% of those evaluated with endoscopy and biopsy, that lower symptoms and older age are the only pre-endoscopy variables significantly associated with histological GVHD, and that this diagnostic strategy only identifies 74% of those patients ultimately treated for GI-GVHD.

We report similar diagnostic sensitivity to those reported in other retrospective studies, but still inferior to those reported in prospective studies, where sensitivities approach 90%. The consistent disparity between retrospective and prospective studies is interesting and not easily explained, given that most institutions report a similar diagnostic approach predominantly using combination endoscopy, and include biopsies performed in macroscopically normal tissue. Rates in the true incidence of GI-GVHD may differ based upon institutional HPCT approach, and upon differences in the clinical threshold used for endoscopy referral.

Our results suggest that the presence of lower gastrointestinal symptoms (such as diarrhoea, abdominal cramps and pain) is the only relevant predictor of subsequently identifying histological GVHD on endoscopy. This is not surprising, as GI-GVHD is classically manifested by lower abdominal symptoms. Severe lower symptoms were highly specific but insensitive, consistent with the experience severe cases account for a minority of GI-GVHD.

However, our results reinforce the poor predictive power of upper symptoms (and by extension, upper endoscopy) for histological GVHD, by showing that upper symptoms were only predictive when associated with co-existing lower symptoms. Upper endoscopy rarely identified discordant findings compared to concurrent lower endoscopy, and only identified an extra 2 (4%) cases of histological GVHD in combination endoscopy. Single upper endoscopy for upper symptoms alone showed the lowest diagnostic sensitivity (14%) for all procedures. Our findings confirm that the distal colon is the site most commonly involved by GI-GVHD, but also illustrate that it is rare for the proximal GIT to be the sole site involved.

Furthermore, clinical severity correlated poorly with reported histological grade, as reported in other studies (3, 4). Possible explanations include sampling error due to patchy bowel involvement by GVHD, or the possibility that histological findings reflect the subsequent “effector” phase of GVHD, which may not be representative of GI-GVHD overall severity. Regardless, the relevance of histological grade in the current context appears questionable.

Interestingly, the presence of upper histological GVHD did not appear to confer adverse survival compared to patients with negative biopsies. This analysis is limited

by the low incidence of isolated upper GVHD, but may suggest a better than expected prognosis when compared to patients with lower GIT GVHD.

A key finding is that early introduction of prednisone did not negatively impact upon the likelihood of identifying histological GVHD. This validates ours and other institutions' practice of not delaying steroid treatment while awaiting confirmatory pathology in patients with a strong clinical suspicion of GI-GVHD and a lack of alternate diagnoses.

Most importantly, our study found that endoscopy and biopsy identifies histological GVHD in only 74% of those ultimately requiring treatment for a clinical diagnosis of GI-GVHD. To our knowledge this finding has not previously been reported, and is a consistent finding in our cohort across different combinations of symptoms and endoscopy procedures. The remaining 26% of patients treated for GI-GVHD despite negative biopsies, best characterised as "discordant" cases, show superior OS compared to "true positive" cases yet inferior OS compared to "true negative" cases (Figure 1).

The explanation for this discrepancy is not clear. Co-existing GVHD in other organs such as skin or liver occurred at similar rates between groups, and repeat endoscopic biopsies (where performed) identified histological GVHD at similar rates between groups. Furthermore, the definitions used for histological and clinical diagnosis appear sufficiently robust as to preclude spurious "over-diagnosis" by clinicians or pathologists in our centre. While the survival difference may represent adverse effects of GVHD therapy in patients not truly requiring therapy, it may plausibly instead illustrate a population with GI-GVHD that is more responsive to therapy.

Nevertheless, regardless of whether 26% of clinical GI-GVHD is "clinically over-diagnosed" or "histologically under-diagnosed," the reality is that this perfectly illustrates a common conundrum in transplantation – the HPCT patient with moderate-severe gastrointestinal symptoms for whom no reasonable diagnosis other than GI-GVHD can be established, despite best practice diagnostic techniques and expertise. Given "discordant" cases have inferior survival to "true negative" cases, there is clearly a need to develop improved diagnostic strategies to better identify GI-GVHD.

A variety of novel techniques are being developed but are not yet ready for universal incorporation into routine practice. Diagnostic molecular imaging using FDG-PET is sensitive for GI-GVHD but nonspecific, and may only have a role in excluding GI-GVHD or in targeting lesions for subsequent endoscopic biopsy (11-13). Blood-based measurement of cytokine biomarkers such as ST2, IL2Ra and TNFR1 has been shown to predict response to anti-GVHD therapy (14-16), however a universally adoptable cytokine panel with high PPV for GVHD has not yet been demonstrated.

The main limitation of our study is its retrospective design, although this is not dissimilar to other studies in this field. Statistical assessments involving the final clinical diagnosis of GI-GVHD may be subject to observer error due to the judgement of individual treating clinicians at the time, which is true of all studies assessing clinical diagnoses.

CONCLUSION

Endoscopy and biopsy remains a valid diagnostic method for GI-GVHD, in combination with clinical judgement. Lower gastrointestinal symptoms and advanced age are the only significant pre-endoscopy variables for predicting histological GVHD. Isolated upper gastrointestinal GVHD is rare, particularly in the absence of lower gastrointestinal symptoms, and shows similar 1-yr OS compared to patients who have negative biopsies. Therefore, upper endoscopy could reasonably be omitted during investigation for GI-GVHD, except where alternative diagnoses are suspected. Overall, endoscopy and biopsy underdiagnoses 26% of clinical GI-GVHD, highlighting a need for research into novel diagnostic strategies.

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The authors declare no competing conflicts of interest.

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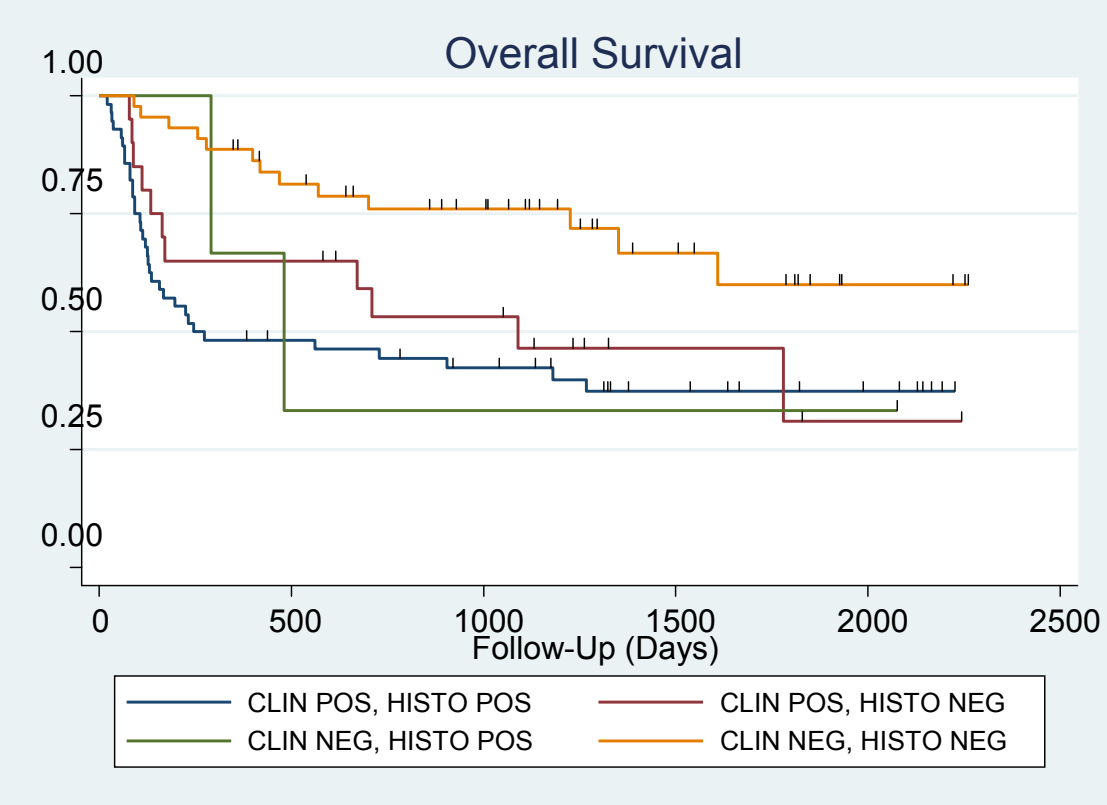
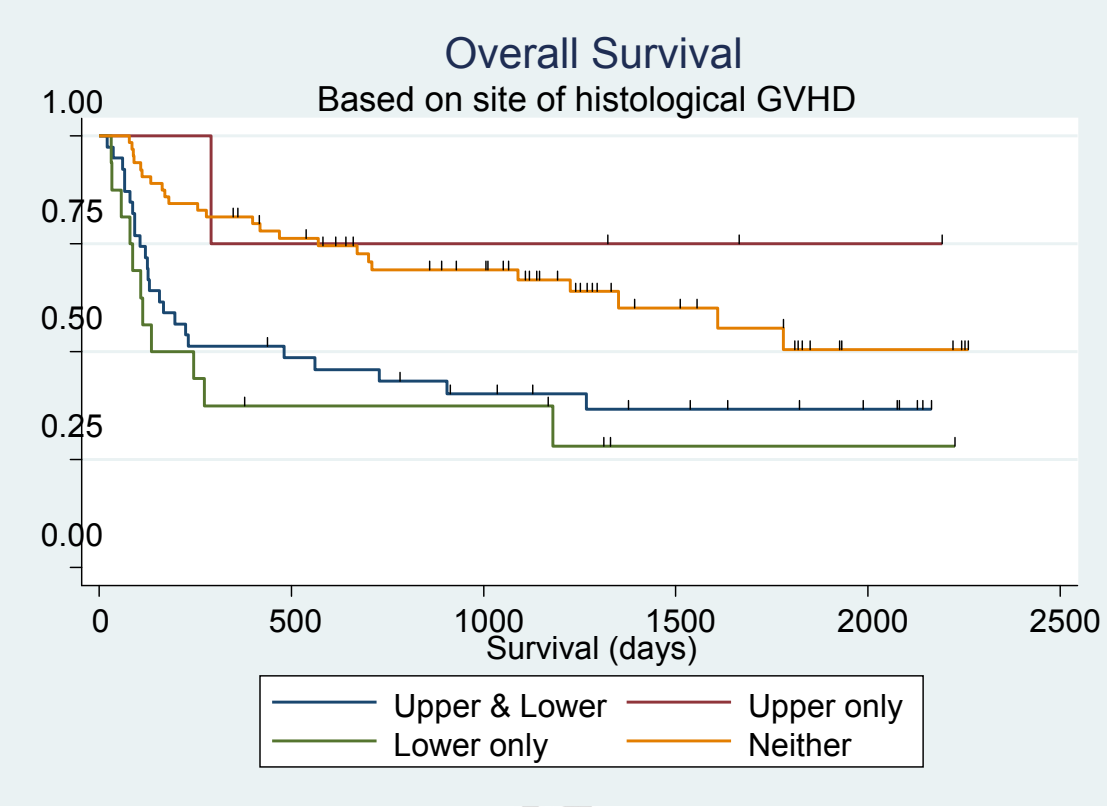
FIGURE 1: OS COMPARING CLINICAL GVHD *VERSUS* HISTOLOGICAL GVHD.



Key: Clin Pos Histo Pos (Histological GVHD and final clinical diagnosis of GI-GVHD), Clin Pos Histo Neg (Histological GVHD but an alternative final clinical diagnosis), Clin Neg Histo Pos (Histology negative for GVHD but final clinical diagnosis was GI-GVHD), Clin Neg Histo Neg (Neither histological GVHD nor a final clinical diagnosis of GI-GVHD).

FIGURE 2: OS COMPARING UPPER VERSUS LOWER GIT INVOLVEMENT.



Key: Upper and Lower (both upper and lower biopsy sites reported as histological GVHD), Lower only (Lower histological GVHD but no upper histological GVHD), Upper only (Upper histological GVHD but no lower histological GVHD), Neither (No upper or lower biopsies reported as GVHD).

TABLE 1: BASELINE CHARACTERISTICS

Characteristic	Number (%)
Number	123
Median age (range)	52 (16-69)
Male sex	63%
Diagnosis:	
- Acute Myeloid Leukaemia	50 (40%)
- Acute Lymphoblastic Leukaemia	29 (24%)
- Myelodysplastic syndrome / Myeloproliferative Neoplasms	28 (23%)
- Lymphoproliferative neoplasms	16 (13%)
Donor:	
- Unrelated	86 (70%)
- Matched sibling	37 (30%)
Conditioning regimen:	
- Myeloablative	46 (37%)
- Reduced intensity	71 (58%)
- Non-myeloablative	6 (5%)

TABLE 2: ENDOSCOPY PROCEDURES PERFORMED.

Findings	Number (%)
Total patients	123
Procedure type:	
Upper endoscopy alone	14 (11%)
Lower endoscopy alone	12 (10%)
Combination upper and lower endoscopy	97 (79%)
Procedure description:	
Upper endoscopy	111
- Oesophagogastroduodenoscopy (OGD)	111 (100%)
Lower endoscopy	109
- Rectosigmoidoscopy	105 (96%)
- Colonoscopy	4 (4%)
Biopsies performed:	
Upper biopsy	110 (99%)
Lower biopsy	109 (100%)
Both upper and lower biopsies	96 (99%*)

**Expressed as a proportion of those who underwent combination endoscopy.*

TABLE 3: HISTOLOGICAL GVHD.

Histological GVHD	Number (%)
Total patients	123
Histological GVHD at any biopsy site	59 (48%)
- Histological Grade III-IV GVHD	19 (15%)
Upper biopsies	110
GVHD	43 (39%)
- Isolated upper GVHD	4 (4%)
Lower biopsies	109
GVHD	55 (50%)
- Isolated lower GVHD	16 (15%)
Combination biopsy	96
GVHD	48 (50%)
- upper GVHD	2 (2%)
- lower GVHD	7 (7%)
- both upper and lower GVHD	39 (41%)

TABLE 4: UNIVARIATE ANALYSIS OF PREDICTORS FOR HISTOLOGICAL GVHD.

Variable	p-value
Age	<0.001
Sex	0.42
Donor type	0.12
CMV match	0.47
Conditioning	0.002
Prednisone >0.5mg/kg on day of endoscopy	0.22
Upper GI symptoms	0.60
Lower GI symptoms	0.003