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Utility of minimally-invasive thoracoscopy for assessment of residual mediastinal lymphoma

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Abstract

Introduction—Patients with primary mediastinal lymphomas frequently present with a residual mass aftercompletion of first-line therapy. While a PET-scan is usually recommended, it fails to distinguish between persistent lymphoma and inflammation. While percutaneous biopsy may have a high diagnostic yield for the initial diagnosis of mediastinal lymphomas, this biopsy has poor accuracy for detecting persistent disease in a residual mass given the heterogeneity of these residual masses.. Because persistent disease has importanttherapeutic implications, we evaluated the role of operative biopsy in detecting lymphoma in the residual mass.

Methods—Between 2009 and 2015, consecutive patients (n=77) undergoing tissue biopsy for initial diagnosis as well as for a PET-positive residual mass were included. Tissue biopsy for a residual mass was repeated until frozen section was diagnostic or at least the mass on the ipsilateral hemi-mediastinum was resected.

Results—Of the initial 77 patients, 34 underwent operative restaging for a residual mass after chemotherapy, while 43 had a complete response. In these 34 patients, operativebiopsy revealed the presence of lymphoma in 53%, predominantly Hodgkins disease and Diffuse Large B Cell type lymphoma. There was no significant difference in tumor volume (51% versus 39%) and adecrease in the PET-SUV_{max} (68% versus 60%) in patients with or with persistent lymphoma. There were no surgical complications and the duration of stay for all patients undergoing thoracoscopy was <24 hours. Residual lymphoma was treated with second-line therapy guided by the pathologic analysis.

Conclusion—A large proportion of patients with residual PET-avidity fter first-line chemotherapy of mediastinal lymphomas have residual disease that can be detected safely using minimally invasive thoracoscopy.

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Introduction

High grade lymphomas constitute a substantial proportion of diseases in the mediastinum, particularly in younger populations nd represent about 12% of all mediastinal tumors and about 25% of tumors found in the anterior mediastinum [1, 2]. The epidemiologic distribution of lymphomas varies depending on the histologic subtype. The two most common subtypes found in the mediastinum are classic Hodgkins lymphoma (cHL) and primary, mediastinal, large B cell lymphoma (PMBL), which is a variant of Diffuse large B cell lymphoma (DLBCL). Both cHL and PMBL are found predominantly in young adults with median ages of 29 and 32, respectively [3, 4]. Other less common subtypes include Gray zone lymphoma and Mucosa-associated lymphoid tissue (MALT) lymphoma, both of which occur more frequently in childhood but are also observed in adults [5, 6]. Treatment of cHL and PMBL varies depending on extent of disease but usually involves systemic chemotherapy with or without radiation for early stages [7, 8]. Prognosis is also dependent on lymphoma subtype and disease staging, but patients with early stage cHL have a high likelihood of obtaining long-term complete remission [9].

The standard of care for assessing disease response to treatment for mediastinal lymphomas localized to the mediastinum has evolved over the past few decades. In a recent publication, the Lugano classification recommended the use of PET-CT to assess the treatment response in FDG-avid lymphomas, which include cHL and DLBCL [10]. International guidelines support this classification and support the utility of post-treatment PET-CT imaging alone to determine complete response, partial response, stable disease, or progressive disease [11]. While the accuracy of PET-CT imaging is well documented [12], PET-CT remains an imperfect technology with limitations [13], particularly in the setting of treated lymphomas [14]. Of particular concern is that PET avidity in the mediastinum may not represent residual disease but rather inflammatory changes resulting from tumor necrosis or other pathologies. In such cases where treatment response is either inadequate or ambiguous based on PET-CT, tissue biopsy provides the gold standard for diagnosis of persistent disease. Core needle biopsies have given variable results in terms of diagnostic yield and are made more difficult by tissue heterogeneity that follows chemotherapy [15, 16]. Iin contrast, minimally invasive thoracoscopic techniquesremain a viable alternative for obtaining diagnostic tissue that avoids the morbidity associated with open procedures [17, 18].

Reported data are sparse regarding the diagnostic outcomes in patient groups who undergo operative re-sampling after first-line chemotherapy and do not assess the utility of minimally invasive techniques, such as video- or robotic thoracoscopy. These techniques allow access to a larger portion of the residual mass which can result in a safer and more thorough tissue sampling, resulting in improved diagnostic yield when restaging is necessary in the setting of persistent PET activity. Detection of residual tumor is important for the patients, because it indicates failure of first-line therapy and can necessitate additional chemotherapy, radiation, or stem cell transplantation. Because the role of minimally invasive thoracoscopic techniques have not been evaluated previously in the restaging of mediastinal lymphoma, the objective of this study was to determine the incidence of residual or recurrent disease in patients undergoing such procedures at our hospital which is a regional referral center for patients with mediastinal lymphoma. Additionally, we correlated the response in PET-

avidity as well as a decrease in tumor size in those with and without confirmed residual disease. Our findings have implications in the adoption of video-assisted or robotic thoracoscopic assessment of PET-positive residual mediastinal masses in patients with primary mediastinal lymphoma after first-line chemotherapy.

Methods

This study is a retrospective study of a prospectively maintained database of patients treated at Northwestern Memorial Hospital with lymphoma. Inclusion criteria included all patients who have undergone operative biopsy for any mediastinal pathology between 1/1/2009 and 12/31/2015, with ages ranging from 18 to 89 years old. Operativetechniques included open procedures such as thoracotomy as well as minimally invasive procedures, including mediastinoscopy, video-assisted thoracoscopic surgery (VATS), or robotic approaches. Subjects meeting these inclusion criteria were identified by a formal query of the institutional Society of Thoracic Surgeons (STS) – General Thoracic Database. The choice of the procedure was dependent on surgeon preference and accessibility of the mass. Subjects included in the final analysis were patients diagnosed with mediastinal lymphoma who underwent first-line chemotherapy with curative intent. Over 300 patients met the entry criteria, and the diagnosis of primary lymphoma in the mediastinum was confirmed in the medical records of 77 patients. Clinical information of these 77 patients was retrieved from electronic health records from time of diagnosis through outcomes aftertheir initial treatment regimen. Variables collected from the review at time of diagnosis included demographic information, initial size of tumor and lymph nodes on CT, SUV of tumor on PET scan, operative procedure for diagnosis, and final pathology. Subsequent variables collected included treatment regimen, sizeon CT and PET SUV aafter treatment, operative procedure for follow-up biopsy, and final pathology. Post-treatment imaging was performed at least 4–6 weeks after the last dose of chemotherapy based on institutional protocols. An experienced nuclear-medicine radiologist in the Northwestern Medicine Department of Radiology evaluated individual patient PET scans and validated the SUVmax for each patient before and after treatment for the purpose of the study. The decreasein SUVmax was defined as the decrease in maximum standard uptake value in the mediastinum from initial PET scan at the time of diagnosis to final PET scan afterchemotherapy as a proportion of the initial SUVmax ($(SUVmax_{initial} - SUVmax_{final})/SUVmax_{initial}$). Additionally, the decrease in the size of the residual mass was determined by CT and was defined as the decresein length of longest axis of lymph node or tumor from initial CT at diagnosis to final CT after treatment as a proportion of the initial tumor size ($(CT_{initial} - CT_{final})/CT_{initial}$). This validation was performed while blinded to the final pathology of each patient. Statistical analysis was performed using SPSS software -- specific analyses included chi square test to compare categorical variables and two sample t test to compare mean values. The Northwestern University Institutional Review Board approved the study.

Results

Of the 77 consecutive patients diagnosed with mediastinal lymphoma after an operative biopsy, 34 patients (44%) underwent operative restaging for a PET-avid residual mass, while 43 (56%) had a complete response with no residual mass and therefore, did not require

repeat biopsy. Table 1 demonstrates the demographic data of the 34-patient cohort, which comprised of 53% male and 82% Caucasians, with a median age of 28 years at time of diagnosis. The type of lymphoma at initial diagnosis included predominantly DLBCL (38%) and Hodgkins (32%) but also included T-cell lymphoma, follicular cell lymphoma, Burkitt lymphoma, and grey zone lymphoma (Table 1). As Table 2 illustrates, initial diagnosis was determined by tissue biopsy of the mediastinal mass or of PET-positive lymph nodes accessible in the cervical or axillary region. All repeat biopsies were of mediastinal tissue, becuse there was no evidence of disease elsewhere, and there was no association between initial diagnostic method and the pathology of post-treatment mediastinal tissue.

The diagnostic outcomes after repeat operative biopsy is also demonstrated in Table 2. Of the cohort of 34 patients with PET-positive residual mediastinal mass, 18 patients (53%) were had persistent lymphoma, whereas 16 (47%) patients revealed no histologic evidence for viable lymphoma. The soperative procedure included repeated biopsies of the specimen until a frozen section diagnosis suggestive of lymphoma was determined by the pathologist. If there was no evidence of lymphoma on the frozen section biopsies, at least half the mass on the hemi-mediastinum was resected to get adequate sampling. In one patient, the entire mass was resected,becausethere were clear anatomic plans with the mediastinal structures. Areas that very vascular were preferred for the biopsy. Pathology descriptors of the tissue samples in these 16 patients included necrosis, granulomatous tissue, reactive thymus, and sarcoidosis. All patients had repeat PET/CT at least 4 weeks aftercompletion of their primary intended treatment. Table 2 demonstrates the changes on PET/CT imaging in these two groups of patients. There was no difference between the mean CT size or mean SUVmax between the two groups prior to or after treatment. Median size on CT (length of longest tumor axis) for the entire cohort was 9.0 cm prior to treatment and 3.0 cm after treatment. Patients detected to have persistent lymphoma had a mean decrease in SUVmax of 0.605 (95% CI [0.455, 0.755]), which was not statistically different than patients without residual lymphoma who had a mean reduction in SUVmax of 0.688 (95% CI [0.519, 0.857], p=0.1). Similarly, patients with residual lymphoma had a mean decrease in CT size of 0.396 (95% CI [0.209, 0.583]), which was not significantly different in patients without residual lymphoma, 0.513 (95% CI [0.309, 0.717], p=0.2).

Minimally invasive techniques were employed in 25 cases for follow-up biopsy. Of these 25 procedures, primary tissue biopsy was obtained using video-assisted thoracoscopic surgery (VATS) in 13 cases, anterior mediastinoscopy in 5 cases, and robotic-assisted thoracoscopic surgery (RATS) in 7 cases. Persistent lymphoma was discovered in 13 (52%) of these cases, whereas no residual lymphoma was found in the other 12 cases. Open procedures were performed in the remaining 9, 5 (55%) of which resulted in residual lymphoma and 4 of which demonstrated no evidence of disease. The results follow an expected equal distribution for both open procedures (p=0.835) and minimally invasive procedures (p=0.740). In 4 minimally invasive cases and one open case, the procedure was preceded by a non-diagnostic percutaneous needle biopsy. Table 3 demonstrates that choice of method of operative biopsy was not associated either with initial diagnostic method (p=0.082) or radiation treatment (p=0.886). The mean size of the aggregate tissue biopsy was similar for both minimally invasive and open procedures (p=0.167). In all cases, the objective of the procedure was to obtain adequate tissue excision for diagnosis rather than to achieve full

resection. In all operative biopsies obtained through minimally invasive techniques, substantial adhesions between lung and mediastinum were noted, and the median duration of the operative procedure was 75 minutes. There were no surgical complications. The duration of stay for all patients was less than 24 hours. In contrast, for open procedures, the median durationof operative procedure for 93 minutes (p=0.01) and the duration of stay was 2.3 ± 1.2 days (p=0.02). None of the 16 patients without residual lymphoma had repeat a repeat biopsy for FDG-avid masses in the 12 months after their procedure or developed disease recurrence in the mediastinum. All patients detected to have residual lymphoma underwent second-line therapy guided by the pathologic analysis. Second-line therapy could be initiated within 2 weeks for all patients undergoing minimally invasive procedure but was avoided for at least 6 weeks for wound healing when open procedures were performed.

Discussion

Mediastinal lymphoma is a common pathology encountered in young healthy patients. Although treatment varies depending on the subtype of lymphoma and extent of disease, most patients undergo chemotherapy with or without radiation. Determining the disease response to treatment depends largely on the characteristics of the PET-CT as established by the Lugano classification, but persistent PET avidity often fails to distinguish residual lymphoma from other benign pathologies. Unfortunately, due to the heterogeneity of the mass after the treatment, image-guided percutaneous biopsies have a poor yield, with diagnostic rates as low as 77% for anterior mediastinal masses and 25% for mediastinal lymphomas specifically [16]. Hence, patients with a PET-positive residual mass often undergo extended surveillance alone. In select cases, operative biopsies can be considered; however, the invasiveness of the open procedures combined with unknown incidence of residual disease has limited the enthusiasm in offering thoracotomy or sternotomy as a modality of incisional biopsy. Hence, minimally invasive video- or robotic thoracoscopic approaches are appealing. Furthermore, because these techniques allow sampling of a broader area and deeper regions of the tissue, these techniques may be preferable to other techniques such as anterior mediastinoscopy. In this study, we demonstrated that operative sampling detects residual lymphoma in > 50% of patients undergoing primary therapy for mediastinal lymphoma who have residual PET-activity in the mediastinal mass. The finding of persistent lymphoma had a clinically important impact on the subsequent management of these patients since all required a second-line therapy. It can be argued that the patients who had a negative biopsy underwent an unnecessary procedure when they had no residual disease; h, this would not have been established without the operative biopsy. Furthermore, as stated above, detection of residual disease in the other half of the patient cohort had substantial therapeutic implications. Becausethe second-line therapy is dependent on further classification of both the residual lymphoma and the genetic analysis, empiric therapy cannot be initiated, and thus, a tissue analysis is imperative. The post-chemotherapy response in PET uptake as well as the decrease in size was not different in the two groups and therefore, not predictive of residual disease. These data are consistent with recent reports demonstrating the inefficacy of PET-scan in predicting disease response in this patient population. Operatiove tissue diagnosis was, therefore, crucial in the management of these patients. Additionally, the operatiove technique was safe and resulted in no complications or

long-term morbidity. Finally, the added assurance of a negative biopsy in the setting of a concerning, PET-avid mass and avoidance of subsequent imaging supports this use of this approach.

While repeat PET scans were performed as early as four weeks aftercompleted treatment according to our institutional standards, some authors suggest waiting at least three months to avoid false positive PET scans caused by radiation-induced tissue injury [19]. In theory, delaying the posttreatment scan or monitoring refractory FDG-avid masses with surveillance could have allowed tissue to heal and potentially decreased the number of patients subjected to an unnecessary procedure. In this cohort,however, only three patients received radiation as part of their primary treatment, two of whom had residual lymphoma, suggesting that radiation-induced injury did not impact these results. Additionally, there is little evidence comparing outcomes in patients who undergo active surveillance versus immediate biopsy of persistently FDG-avid masses, nd the prognosis of refractory disease is worsened by advanced staging [20], suggesting that timely detection and salvage treatment are critical to prolong survival.

A major concern for performing an operative biopsy is the risk of potential complications and delay in the institution of second-line therapy. While this may be true for the traditional open procedures, such as thoracotomy and sternotomy, thoracoscopic procedures as shown in our study are highly effective, safe, less painful, and do not result in substantial delay in the initiation of post-operative chemotherapy. There were no wound complications in any of the patients undergoing biopsy using minimally invasive surgery, and there were no readmissions. In fact, our practice is to discharge patients the same day of operation after thoracoscopy and have not observed any 30-day readmissions related to an operative complication in this cohort.

Minimally invasive techniques were safe and have a similar yield as open procedures and should be considered preferentially for restaging the mediastinum afterprimary chemotherapy if a PET-avid residual mass is detected. The choice of a minimally invasive technique for each patient was determined largely by the preference of the surgeon given the location of tumor on imaging. Anterior mediastinoscopy which was utilized in five cases is an effective method for accessing masses adjacent to the airway, particularly in upper paratracheal lymph nodes superior to the aortic arch. Thoracoscopy using VATS and RATS provides a broader visualization of the anatomic field and greater versatility for the surgeon to access tissue essentially anywhere in the mediastinum. Cervical mediastinoscopy is usually not employed, because the lymphomas affect anterior mediastinum. Core needle biopsy was attempted in seven cases due to its appealing minimal invasiveness and history of success for some patients in establishing initial diagnosis, however, only two of the seven procedures yielded diagnostic results, while the other five cases were unsuccessful and required a follow-up operative biopsy. These results support previously reported findings showing that needle biopsies are an unreliable method of tissue diagnosis for these patientsafter treatment. None of the minimally invasive operations necessitated conversion to open surgery. Rather, the open procedures were elected based on tumor presentation, procedure objectives, and surgeon comfort. Given the improved outcomes and equivalent

diagnostic yields of the minimally invasive operations, thes minimally invasive techniques should represent the preferred strategy for future cases.

The secondary objective of the study was to re-assess for a difference in response to therapy demonstrated on PET-CT imaging between the group of patients with persistent lymphoma and the group of patients in remission. Response on imaging was characterized in two ways: 1) as the percent decrease in PET-avidity measured as the maximum standard uptake value, and 2) the percent decrease in CT size measured as the maximum length of the tumor. Mean percent decresein SUVmax was 61% (95% CI [45.5, 75.5]) for patients with residual lymphoma and 69 % (95% CI [51.9, 85.7]) in patients without lymphoma. Mean percent decrease in CT size 40% (95% CI [20.9, 58.3]) in patients with residual lymphoma and 51% (95% CI [30.9, 71.7]). By both criteria, the disease response was more marked in patients without residual lymphoma which is the expected trend, however, the difference in disease response between the two groups was not statistically significant. It is undetermined whether the lack of syttisticalsignificance represents a failure of statistical power or a truly nonexistent distinction. Nevertheless, our results demonstrate an inability to reliably distinguish between residual lymphoma or treatment response based on a retrospective analysis of changes in PET -CT imaging. These findings, therefore, further support tissue biopsy as a necessary intervention to establish this distinction.

Due to the retrospective nature of our study at a single institution, there are some limitations that warrant consideration. While the study cohort is fairly homogenous in terms of its demographic attributes, it comprises substantial heterogeneity in the treatment regimens used in this cohort of patients. Patients with all lymphoma subtypes were included to represent a larger study population. Because patients in the cohort had various lymphoma subtypes and different staging variables within those lymphoma subtypes, specific chemotherapy regimens differed. Hence, we are unable to distinguish the utility of operative biopsy in the different lymphoma subtypes. Differences in treatment response between different lymphoma subtypes might alter the diagnostic yield of operative biopsy which should be considered in future studies. Nevertheless, our cohort was comprised predominantly of Hodgkins lymphoma and Diffuse Large B Cell Lymphoma, the two most frequently types arising in the mediastinum which mitigates such a bias.

In conclusion, this study supports the use of operative techniques for tissue diagnosis in patients with mediastinal lymphoma who demonstrate persistent PET-avidity after initial treatment. This support is grounded both in the equitable incidence of malignant and benign outcomes on post-treatment biopsy as well as the inability to reliably distinguish persistent lymphoma from inflammation based on PET-CT imaging and image-guided biopsy. Therefore, while the current standard of care is surveillance alone in patients with residual PET activity, our data suggest strongly that a large number of these patients have residual lymphoma which can be diagnosed safely and accurately using minimally invasive thoracoscopic approachesallowing for expeditious transition to salvage therapy. Future studies have the opportunity to confirm these findings with larger study cohorts across multiple institutions.

SURGICAL STAGING IS SUPERIOR TO PET SCAN FOR ASSESSMENT OF DISEASE RESPONSE FOLLOWING CHEMOTHERAPY FOR MEDIASTINAL LYMPHOMA

DISCUSSANT

DR. JEFFREY SUSSMAN (Cincinnati, OH): Good morning. Thank you to the Association for the pleasure of discussing this paper.

The authors retrospectively reviewed their single institutional prospectively maintained database to examine their experience with mediastinal lymphoma and restaging after initial therapy. In particular, approximately half the 77 patients identified had persistent PET positive mediastinal masses and approximately half of these PET positive masses showed no viable cancer. Additional therapy could be administered to the PET positive patients that were pathologically positive and with whom minimally invasive results may have no delay in reinitiating therapy and no complications.

Although surgery is not the curative modality in these patients, surgeons can still play a role in diagnosis, venous access device placement, and as you discussed, restaging. It is therefore important that surgical care is cost and time efficient with minimum morbidity as not to interfere with subsequent systemic radiation therapies.

This is a nice paper that reinforces the important role a surgeon can still play in a world of non-surgeon interventionalists. Sometimes the quickest and most efficient method of obtaining adequate diagnostic tissue is with a well-performed surgical procedure such as you described with your colleagues at Northwestern.

I do have several questions.

1. As I’m a surgical oncologist, and not a thoracic surgeon, forgive my ignorance, but you have no operative complications and a length of stay of less than 24 hours. Can I reasonably expect the average thoracic surgeon to have such excellent results?
2. On average, you showed no difference in size or SUV maximum on your PET scans. Were there any more extreme cutoffs that were predictive? In other words, were there PET positive results that you did not feel you need a surgical biopsy, or is there any role for active observation and follow-up PET scan?
3. Some authors have recommended that end-of-treatment PET scan not be obtained until after six to eight weeks following chemotherapy or eight to 12 weeks following radiation therapy to allow for the treatment-related inflammation to resolve. Your institutional policy called for a PET scan at four to six weeks post-treatment. Could this contribute to your rate of PET positive but pathologically negative results?

4. What was the false negative rate of surgical biopsy? In other words, how often were mediastinal occurrences still seen on follow-up despite a negative surgical biopsy?

5. Is there concern for tumor spread to sites outside the mediastinum depending on the surgical approach? How do you decide which minimally invasive approach to use -- thoracoscopic, mediastinal, or robotic?

6. Finally, what is the role for image or endobronchial guided fine needle or core biopsy? How often is insufficient tissue obtained leading to either additional interventions or the result falsely interpreted as a complete response?

I enjoyed your presentation. Thank you for your well-presented presentation as well as the paper in advance.

CLOSING DISCUSSANT

MR. LIAM KANE: Those are great points for discussion. In terms of whether or not we can expect these surgical results in the average surgeon, the overall complication rate I have seen in minimally invasive techniques used in the thorax is around 3% to 4%. The center for direct surgery did a pretty large series study looking at VATS procedures between 1996 and 2008. We found that the most common complication was prolonged air leak that happened in about four to five percent of patients. Then other complications, bleeding, atelectasis, infection, were all less than 2% and the overall conversion to thoracotomy was about 1.5%.

That said, there are other studies that have shown that conversion thoracotomy is as high as 10%. The reasons for that could be problems with anesthesia, trouble accessing the tissue, insufficient resection, and then bleeding or any other complication. Where the average surgeon falls under that range is difficult to say. It probably depends on how well their training is.

It’s definitely important to have an experienced, comfortable surgeon when performing these techniques, especially after chemotherapy and radiation when there’s a lot of inflammation, fibrosis, and visualization can be difficult.

You asked about whether there were any extreme cutoffs. Low sample size makes it a little bit difficult. I have to go and reevaluate the data. Speaking anecdotally from what I remember, there were a few patients, one or two patients, whose reduction in standard uptake value was very unimpressive, 5% or 10%, and they did have a lymphoma on repeat surgical biopsy. But in order to even out the percentage, of course, there are patients with larger reduction uptake value that also had residual cancer. So, ideally, with the larger sample size, we would be able to maybe find a cut-off like around the 80%, 90% maybe if there are a significant number of patients that had no residual lymphoma, but based on these results it’s difficult to say.

The guidelines recommend repeat surgical biopsy for anyone that’s going to undergo further chemotherapy. So the only argument, I guess, for continued surveillance would be under patients who had large percentage reduction uptake value, and again maybe pulling larger cohorts together could help with that.

You also mentioned that four- to six-week timetable. I agree there are studies that show that when a patient receives radiation, radiation-induced lung disease, other radiation-induced inflammation, fibrosis, can happen up to three months after treatment, and I think it's certainly worth consideration for an institution to extend the four to six weeks PET scan to longer timetable, like 10 to 16 weeks, given that so many of our patients did have benign pathology, many of whom were necrosis-induced from radiation.

You mentioned, I believe, the concern for tumor seeding. I have seen that referenced with patients with encapsulated thymomas receiving percutaneous biopsies. I haven't seen it referenced with minimally invasive techniques or in regards to mediastinal lymphoma. Of course, the way around seeding would be to perform an excisional or a full resection, but typically patients who have mediastinal lymphoma don't undergo resections. So I would have to look more into that to see whether or not that's an issue.

In terms of how the method of surgery is chosen, it typically involves a bunch of factors -- patients, location of the tumor, presumptive diagnosis, lymphoma, and preference and comfortability of the performing physician.

Many surgeons from what I have read are hesitant to perform these minimally invasive techniques if the patient has recently undergone chemotherapy or radiation just because of all the fibrosis and strictures associated with the mass. That said, with an experienced surgeon, I think it's a pretty viable alternative to more open techniques given the reduced morbidity.

In terms of which minimally invasive technique to use, if the patient has a mass that's substernal, the Chamberlain procedure is a good choice. A good alternative is the robotic approach, which seems to be the sort of go-to procedure. It provides excellent anatomic view and access to the tissue virtually anywhere in the mediastinum.

Finally, I just want to comment on whether there is a role for core needle or fine needle aspiration? A 2015 study out of MGH looked at 52 patients that had anterior mediastinal masses who had core needle biopsies, and 40 of those patients had a diagnostic yield from the core needle biopsy, so that's 77%. When fine needle aspiration was done alone, I think even fewer, I think 60% of those patients had diagnostic yield. The diagnostic yield was even lower when the patient had lymphoma, so 22 of those patients had lymphoma and 13 of those patients had diagnostic yield from CT. All the rest of the patients required surgical excision for the biopsy.

So I would say the preference is for minimally invasive surgical techniques over core needle biopsy for mediastinal lymphoma.

DISCUSSANT

DR. MARGO SHOUP (Warrensville, IL): I, like Dr. Sussman, am a surgical oncologist, not a thoracic surgeon, but we see this not infrequently with other cancers such as metastatic colon cancer of the liver where they get their chemotherapy and enter the patient to surgery,

and the PET scan turns out to have no activity after the chemo, but the resection clearly shows that there's tumor there.

On the patients that you have in your study, what happened to those patients who actually did have residual lymphoma, despite being PET negative or very good response on PET scan? Did they go on to get second-line chemo? How would they be followed then if the PET scan is not that accurate? Or did any of the patients undergo surgical resection of lymphoma? It's just not thought of as a surgical disease. I would be curious to see what happened with these patients.

CLOSING DISCUSSANT

MR. LIAM KANE: All the 34 patients included in this study had residual PET avidity. Their score was 4 or 5, so I didn't follow any patients who had negative PET scans, and then were determined to have residual lymphoma. Basically, the recommendation, if their PET scan was negative, they were just monitored by continued surveillance, so they didn't have any repeat surgery that was done, to my knowledge, but it's probably worth looking into to see if they did have recurrence that happened in subsequent PET scans.

DISCUSSANT

DR. ROGER KEITH (Saskatoon, CN): I would like to commend you on your presentation. I want to ask you, of your minimally invasive surgical procedures, what number were done by mediastinoscopy. The mediastinoscopy is perhaps the best way to assess the mediastinal lymph nodes, or an anterior mediastinotomy in case of a large substernal presence of lymph nodes.

What percentage of your diagnostic procedures were mediastinoscopy? Mediastinoscopy or surgical biopsy gives you a good sample now in the days of tailoring chemotherapy to a specific diagnosis or detecting tissue marker. I think the mediastinoscopy we found to be very helpful, and we have very little use for needle biopsy.

CLOSING DISCUSSANT

MR. LIAM KANE: The predominant method that was used was VATS or Robotic VATS, and a few Chamberlain procedures. Mediastinoscopy did not make up many of the invasive techniques used but I would have to go back and look to get an exact number. That's a great point. Thank you.

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References

1. Chen L, Wang M, Fan H, Hu F, and Liu T, Comparison of pediatric and adult lymphomas involving the mediastinum characterized by distinctive clinicopathological and radiological features. Sci Rep, 2017 7(1): p. 2577. [PubMed: 28566711]

2. Maeshima AM, Taniguchi H, Suzuki T, et al., Distribution of malignant lymphomas in the anterior mediastinum: a single-institution study of 76 cases in Japan, 1997–2016. Int J Hematol, 2017 106(5): p. 675–680. [PubMed: 28921451]

3. Nguyen LN, Ha CS, Hess M, et al., The outcome of combined-modality treatments for stage I and II primary large B-cell lymphoma of the mediastinum. Int J Radiat Oncol Biol Phys, 2000 47(5): p. 1281–5. [PubMed: 10889382]

4. Huang X, Nolte I, Gao Z, et al., Epidemiology of classical Hodgkin lymphoma and its association with Epstein Barr virus in Northern China. PLoS One, 2011 6(6): p. e21152. [PubMed: 21695175]

5. Wilson WH, Pittaluga S, Nicolae A, et al., A prospective study of mediastinal gray-zone lymphoma. Blood, 2014 124(10): p. 1563–9. [PubMed: 25024303]

6. Weissferdt A and Moran CA, Primary MALT-type lymphoma of the thymus: a clinicopathological and immunohistochemical study of six cases. Lung, 2011 189(6): p. 461–6. [PubMed: 21989494]

7. Zinzani PL, Stefoni V, Finolezzi E, et al., Rituximab combined with MACOP-B or VACOP-B and radiation therapy in primary mediastinal large B-cell lymphoma: a retrospective study. Clin Lymphoma Myeloma, 2009 9(5): p. 381–5. [PubMed: 19858058]

8. Brusamolino E, Lazzarino M, Orlandi E, et al., Early-stage Hodgkin's disease: long-term results with radiotherapy alone or combined radiotherapy and chemotherapy. Ann Oncol, 1994 5 Suppl 2: p. 101–6. [PubMed: 7515642]

9. Klimm B, Goergen H, Fuchs M, et al., Impact of risk factors on outcomes in early-stage Hodgkin's lymphoma: an analysis of international staging definitions. Ann Oncol, 2013 24(12): p. 3070–6. [PubMed: 24148816]

10. Cheson BD, Fisher RI, Barrington SF, et al., Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol, 2014 32(27): p. 3059–68. [PubMed: 25113753]

11. Barrington SF, Mikhaeel NG, Kostakoglu L, et al., Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol, 2014 32(27): p. 3048–58. [PubMed: 25113771]

12. Karls S, Shah H, and Jacene H, PET/CT for Lymphoma Post-therapy Response Assessment in Other Lymphomas, Response Assessment for Autologous Stem Cell Transplant, and Lymphoma Follow-up. Semin Nucl Med, 2018 48(1): p. 37–49.

13. Roberts PF, Follette DM, von Haag D, et al., Factors associated with false-positive staging of lung cancer by positron emission tomography. Ann Thorac Surg, 2000 70(4): p. 1154–9; discussion 1159–60. [PubMed: 11081861]

14. Nogami M, Nakamoto Y, Sakamoto S, et al., Diagnostic performance of CT, PET, side-by-side, and fused image interpretations for restaging of non-Hodgkin lymphoma. Ann Nucl Med, 2007 21(4): p. 189–96. [PubMed: 17581717]

15. Iguchi T, Hiraki T, Matsui Y, et al., CT fluoroscopy-guided core needle biopsy of anterior mediastinal masses. Diagn Interv Imaging, 2017.

16. Petranovic M, Gilman MD, Muniappan A, et al., Diagnostic Yield of CT-Guided Percutaneous Transthoracic Needle Biopsy for Diagnosis of Anterior Mediastinal Masses. AJR Am J Roentgenol, 2015 205(4): p. 774–9. [PubMed: 26397325]

17. Paul S, Altorki NK, Sheng S, et al., Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. J Thorac Cardiovasc Surg, 2010 139(2): p. 366–78. [PubMed: 20106398]

18. Paul S, Isaacs AJ, Treasure T, Altorki NK, and Sedrakyan A, Long term survival with thoracoscopic versus open lobectomy: propensity matched comparative analysis using SEER-Medicare database. BMJ, 2014 349: p. g5575. [PubMed: 25277994]

19. Choi YW, Munden RF, Erasmus JJ, et al., Effects of Radiation Therapy on the Lung: Radiologic Appearances and Differential Diagnosis. Radiographics, 2004 24(4): p. 985. [PubMed: 15256622]

20. Josting A, Franklin J, May M, et al., New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. J Clin Oncol, 2002 20(1): p. 221 [PubMed: 11773173]

Table 1.

Demographic of Study Cohort

	Residual lymphoma	No residual lymphoma	P value
Age			
Average age	38 +/− 19	33 +/− 13	0.398
Sex			
Male	56% (10)	50% (8)	0.824
Female	45% (8)	50% (8)	0.602
Race			
White	89% (16)	75% (12)	0.656
Black	(1)	(1)	0.933
Histology			
DLBCL	39% (7)	8	0.948
Hodgkins	39% (7)	25% (4)	0.477
T cell	(0)	25% (4)	0.034
Follicular cell	167% (3)	(1)	0.377

Note. T test performed to compare average age between patients with and without residual lymphoma. Chi square test performed for remaining variables based on null hypothesis that they are equally distributed in patients of both outcome groups. Patients with T cell lymphoma were more likely to have benign pathology on repeat biopsy.

Table 2.

Post-treatment Changes in Size and Avidity of Tumor on PET/CT

	Residual lymphoma	No residual lymphoma	P value
Total patients	18	16	0.731
Initial diagnostic procedure			
Axillary lymph node biopsy	1	3	0.317
Cervical lymph node biopsy	6	2	0.157
Core needle mediastinal	5	7	0.564
procedure			
Minimally invasive surgery	6	4	0.480
Imaging characteristics			
Mean pretreatment SUVmax	19 (12.2–27.2)	312.9 (8.2–17.6)	0.155
Mean posttreatment	9 (4.4–13.6)	5 (3.0–6.7)	0.136
SUVmax			
Mean pretreatment CT size	9 (6.3–11.7)	8 (5.9–10.9)	0.738
Mean posttreatment CT size	5 (3.1 – 6.3)	4 (2.5–4.7)	0.282
Imaging changes			
Mean reduction in SUVmax	61% (45.5–75.5)	689% (51.9–85.7)	0.478
Mean reduction in CT size	40% (20.9–58.3)	51.% (30.9–71.7)	0.418
Method of tissue sample			
Minimally invasive	11	12	0.835
Open procedure	5	4	0.740
Core needle biopsy	2	0	0.158

Note. CT size defined as length (cm) of longest tumor axis. Mean reduction in SUVmax calculated as ($SUVmax_{initial} - SUVmax_{final}$)/$SUVmax_{initial}$. Mean reduction in CT size calculated as (($CT_{initial} - CT_{final}$)/$CT_{initial}$). Open procedures include thoracotomy, sternotomy, transcervical, transbronchial. Minimally invasive procedures include mediastinoscopy, VATS, robotic. Chi square test p value calculated for categorical variables and two sample t test p value calculated to compare means.

Table 3.

Potential Determinants of Biopsy Method

	Minimally invasive	Open	P value
Total	25	9	
Mean aggregate size of tissue biopsy	2.5 cms	2.9 cms	0.167
Pretreatment core needle biopsy	10	2	0.320
Pretreatment minimally invasive biopsy	6	2	0.082
Treatment involved radiation	2	1	0.886
Preceded by non- diagnostic needle biopsy	4	1	0.756

Note. T test performed for mean size of tissue biopsy obtained from minimally invasive and open techniques. Chi square p value based on null hypothesis that choice of surgical biopsy method was unaffected by various pre-biopsy factors.