The Role of the Gallium Scan in Primary Extranodal Lymphoma

Raihan Hussain, David R.H. Christie, Val Gebski, Michael B. Barton and Simon M. Gruenewald
Departments of Nuclear Medicine and Radiation Oncology, Westmead Hospital, Westmead, Australia

The purpose of this study was to examine the factors influencing gallium scan positivity for patients with primary extranodal lymphoma and to examine the role of the gallium scan in staging the disease and assessing response to initial treatment. **Methods:** Ninety-two patients with extranodal lymphoma who had a gallium scan were reviewed. The influences of tumor site, size, grade and the presence of clinically detectable disease after biopsy on the rate of gallium scan positivity were analyzed. The role of the gallium scan in staging and selecting treatment was assessed. Nineteen patients had a gallium scan to assess their response to treatment, and its predictive value was reviewed. **Results:** The overall gallium scan positivity (sensitivity) rate was 70%. This rate was low in patients whose extranodal lymphoma occurred in skin, intestine and testis, or was low grade (0%–25%). When these patients were excluded, the rate rose to 88%. Gallium scan positivity was not related to the presence of clinically detectable disease after biopsy and there was insufficient data about tumor size to determine a relationship. The gallium scan increased the disease stage in six patients (7%) and changed the initial treatment in six patients (7%). The gallium scan became negative in 15 (79%) of those patients who had a gallium scan to assess their response to treatment. All but two of these patients remain alive with a median follow-up of 3.75 yr. **Conclusion:** The gallium scan was rarely positive for patients with skin, intestinal, testicular and low-grade lymphomas, but was otherwise comparable to lymphoma arising in lymph nodes. The result affected staging or treatment in seven patients (8%). After treatment, an initially-positive gallium scan usually became negative, a conversion associated with a favorable outcome.

Key Words: gallium; extranodal lymphoma; radiotherapy; chemotherapy

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The gallium scan has a well-documented role in nodal lymphoma, for both disease staging and assessing treatment response, but is yet to be established in extranodal lymphoma (*1–3*). Reports on the use of the gallium scan in some extranodal sites have been published, including skin (*4*), gastrointestinal tract (*5,6*), Waldeyer's ring (*7*), bone (*8–10*), liver (*11*) and thyroid (*12*), but no overall comparison has been made between nodal and extranodal lymphomas, and variations in the role of the gallium scan between different types of extranodal lymphoma have not been assessed.

The overall gallium scan positivity rate for non-Hodgkins lymphoma arising in lymph nodes is 75%–90%, slightly lower than Hodgkin's disease (85%–95%) (*1–3,13*). Nearly all extranodal lymphomas are non-Hodgkins lymphomas and, therefore, one might expect the detection rate for extranodal lymphoma to be comparable to this lower rate. The histologic and clinical features of extranodal lymphoma vary widely with site of origin, and it is likely that the clinical utility of the gallium scan would vary between them. For example, extranodal lymphoma arising in the skin is commonly low grade and T-cell type, whereas Burkitt's lymphoma arising in the mandible is usually high grade and tends to occur in children. The extranodal lymphomas are a heterogeneous group of tumors whose natural history, clinical features and treatment response are clearly different to nodal non-Hodgkins lymphoma. The purpose of this study was to describe the relationships between the gallium scan positivity of an extranodal lymphoma and its site, size, histological grading or prognosis and whether the gallium scan assists in either staging the disease or assessing its response to treatment.

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For correspondence or reprints contact: Simon M. Gruenewald, Department of Nuclear Medicine, Westmead Hospital, Westmead, NSW 2145, Australia.

MATERIALS AND METHODS

Study Design

The two databases at this hospital that contain information about patients with extranodal lymphoma undergoing a gallium scan (from the radiation oncology and nuclear medicine departments) were searched to identify patients who had a diagnosis of primary extranodal lymphoma, had a gallium scan for staging and were treated with curative intent during a 15-yr period (1979–1994). Lymphomas from all extranodal sites were considered. Each patient's medical records were reviewed. This search yielded 92 patients (48 men, 44 women; mean age 55 yr; age range 15–85 yr). The median length of follow-up was 4.3 yr (range 2 to 125 mo). The intermediate histological grade was predominant (n = 57, 62%) as represented in Table 1. Extranodal lymphomas occurred at many different sites, as shown in Table 2.

The extent of disease shown on the gallium scan was compared with information gained by the other conventional, gold standard methods, namely clinical findings, plain radiographs, CT scanning of chest, abdomen, pelvis and the primary tumor, where appropriate and bone marrow examination. The gallium scan was considered to show more extensive disease than the standard methods of assessment if areas of uptake that were likely to represent further disease were demonstrated in sites that would otherwise have remained unknown. Measurements of primary tumor size were recorded from measurements made at the time of clinical examination or initial radiological assessment by CT scans of the primary tumor. Measurements of tumor size were only available in 29 patients. The size ranged from 1 cm to 25 cm, the majority (n = 15, 52%) were between 2 cm and 5 cm.

The likelihood of clinically detectable disease being present after biopsy of the primary tumor was estimated from the description of the resection margins in the biopsy reports. Fifty percent of cases were considered likely to have clinically detectable disease at the primary site after biopsy, 19% were considered unlikely and in 31% it was not able to be determined.

The effect of the gallium scan result in changing the Ann Arbor disease stage was recorded. The effect of the gallium scan result on the choice of treatment method (chemotherapy, radiotherapy or both) or the extent of treatment by each modality (number of cycles of chemotherapy, size of radiotherapy fields) also was recorded. The influence of factors on gallium scan positivity was assessed using logistic regression analysis. Survival times were compared using the log-rank method.

TABLE 1
Histological Grading of Extranodal Lymphomas

Grade	No. of patients (% of total)	Gallium positivity (% of grade)
Low	12 (13%)	3 (25%)
Intermediate	57 (62%)	45 (79%)
High	4 (4%)	4 (100%)
Unclassified	19 (21%)	12 (63%)
Total	92 (100%)	64 (70%)

Gallium Scanning

Each gallium scan was performed using multiple overlapping planar views 48 hr or 72 hr following intravenous administration of 300 MBq ^{67}Ga-citrate. Additional views were obtained up to 7 days after injection if required. All studies were acquired on a large field-of-view gamma camera equipped with a medium-energy collimator. Twenty-percent windows were placed symmetrically around each of the three main photopeaks of ^{67}Ga (93, 184 and 296 KeV). Images were acquired for 600,000 counts on the posterior chest image and then other views were taken for the same time. SPECT images were not acquired.

Patient Assessment and Treatment

Staging assessments included physical examination, chest radiograph, full blood count, biochemical analysis and bone marrow biopsy. Seventy-one patients also had a staging CT scan of chest, abdomen and pelvis. These were performed using standard intravenous and oral contrast with 1-cm slices every 1–1.5 cm. Disease stage was assigned according to the Ann Arbor system (*14*). All patients had biopsies, and the histological grade was assigned according to the working formulation (*15*) into low, intermediate and high grades.

TABLE 2
Locations of Site-Specific Primary Extranodal Lymphoma

Site	No. of patients (% of total)	Gallium positivity (% of site)
Oral/pharyngeal	16 (17%)	13 (81%)
Stomach	13 (14%)	11 (85%)
Skin	8 (9%)	2 (25%)
Salivary glands	8 (9%)	7 (88%)
Bone	8 (9%)	6 (75%)
Intestine	5 (5%)	1 (20%)
Thyroid	5 (5%)	4 (80%)
CNS	5 (5%)	4 (80%)
Breast	4 (4%)	3 (75%)
Testes	2 (2%)	0 (0%)
Others	18 (21%)	13 (72%)
Total	92 (100%)	64 (70%)

All patients received radiotherapy, chemotherapy or both, except one patient with skin lymphoma who had surgical excision alone. Radiotherapy was given by either 300 kilovoltage or 6 megavoltage photon beams, once daily, five times per week to total doses of 25–50 gray. Chemotherapy consisted of CHOP (cyclophosphamide, Adriamycin, vincristine and prednisolone) or one of its variants, for three to eight cycles.

RESULTS

Factors Affecting Gallium Scan Positivity

The analysis of factors determining gallium scan positivity revealed a significant association between gallium scan positivity and histological grade ($p = 0.015$). There was no significant association between the presence of clinically detectable disease after surgery and gallium scan positivity. In 17 patients with no clinically detectable disease postbiopsy, the gallium scan was positive in nine patients. There was insufficient data on tumor size to permit statistical testing of any association. Similarly, there were too many different sites of disease (Table 2) to permit statistical analysis, but the proportion of patients with a positive result was approximately constant in all sites except skin, intestine and testis where the rates of gallium scan positivity were low (0%–25%). The overall gallium scan positivity rate was 70%, but this rose to 88% if patients with skin, intestine, testicular or low-grade lymphomas were excluded.

Results of the Gallium Scan When Used in Staging

Seventy-one patients had both a gallium scan and a CT scan for staging. In 46 patients (65%), the studies produced similar results (both negative in 13, both positive in identical sites in 33). In 13 patients (18%), the gallium scan showed more extensive disease than the CT scan, and the CT scan showed more extensive disease than the gallium scan in 12 patients (17%). Patients whose stage or treatment were affected by the result of the gallium scan are listed in Table 3. The use of gallium scan for staging resulted in increasing the assigned stage of six patients, in five of these the treatment was altered accordingly. In one other patient, the radiation field was extended to include mediastinal nodal involvement detected by gallium scan, which did not result in changing the disease stage. CT scans were not performed in 21 patients, in 18 of these the gallium scan was positive. The 5-yr survival rate for all patients was 58%, and there was no significant difference in survival between those who were gallium scan positive and those gallium scan negative (59% versus 58%, $p = 0.521$). Over half the patients received radiotherapy alone, while nearly half received chemotherapy alone or in combination with radiotherapy (Table 4). The proportion of gallium scan-positive patients who received combined treatment was higher than the propor-

TABLE 3
Patients Whose Gallium Scan Resulted in Upstaging or Treatment Modification

Patient no.	Age (yr)	Sex	Primary site	Gallium positive site	CT	CT (on review)	Upstaged	Treatment changed
1	60	F	Breast	Rib, femur	–	–	Yes	Yes
2	78	F	Submandibular gland	Perihilar LN	–	–	No	Yes
3	38	F	Oropharynx	Iliocaecal LN	–	+	Yes	Yes
4	32	M	Tonsil	Epigastrium	–	+	Yes	Yes
5	84	F	Thyroid	Iliofermoral LN	nd	nd	Yes	No
6	49	M	Tonsil	Cervical LN	nd	nd	Yes	Yes
7	32	M	Stomach	Paraaortic LN	nd	nd	Yes	Yes

F = female; M = male; LN = lymph node; + = positive; – = negative; nd = not done.

TABLE 4
Treatment and Gallium Scan Positivity

Treatment	No. of patients (% of total)	Gallium positivity (% of treatment group)
Radiotherapy alone	50 (54%)	31 (62%)
Chemotherapy alone	20 (22%)	16 (80%)
Both	21 (23%)	17 (81%)
No treatment	1 (1%)	0 (0%)
Total	92 (100%)	64 (70%)

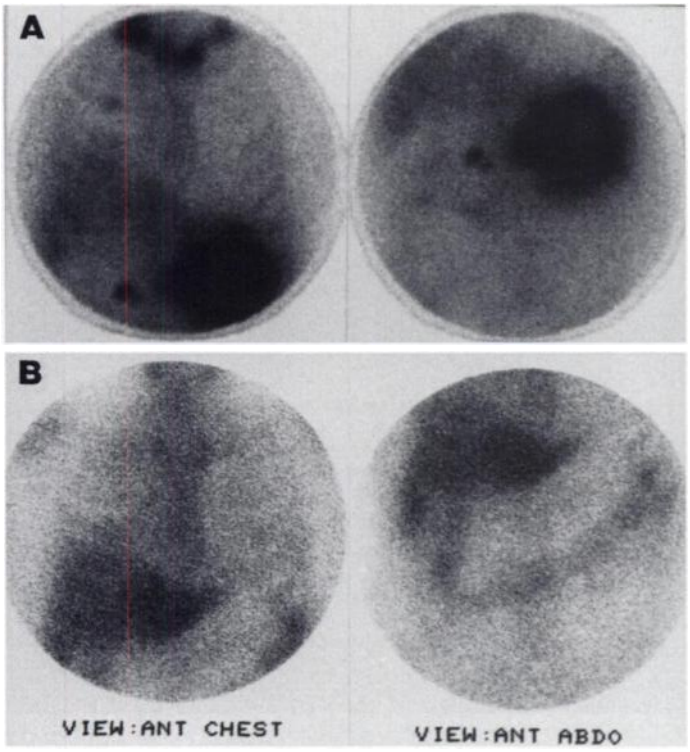

FIGURE 1. (A) Pretreatment and (B) post-treatment gallium scans showing complete resolution of abnormal uptake in the stomach.

tion of gallium scan-negative patients (17% versus 4%), probably reflecting more advanced disease.

The Gallium Scan in Assessing Treatment Response

Nineteen patients had a gallium scan to assess disease response after initial treatment. The gallium scan was initially positive in all 19 patients and became negative after treatment in 15 patients (Figs. 1 and 2). All but two (86%) of the patients who became gallium scan negative remain alive with a median follow-up of 3.75 yr. This compares favorably with the remainder of the study population. Five of these 15 patients subsequently relapsed at the primary tumor site and two relapsed at other sites. No difference in prognosis could be demonstrated between patients who became gallium scan negative or remained gallium scan positive after treatment as only four patients remained positive. Of the four patients with positive post-treatment scans, two proceeded to radiotherapy on the basis of the result, but were not rescanned. Three of the four patients remain alive without disease at 26, 27 and 45 mo of follow-up, one of these was rescanned again at 6 mo and no abnormality was found. The fourth patient died of disseminated disease 6 mo after treatment, however, her abnormal uptake on the post-treatment scan was more likely to be due to perforation of the stomach rather than recurrent disease.

DISCUSSION

Our patient population and their tumors were consistent with other reports of extranodal lymphoma. The gallium scan positivity rate of the extranodal lymphomas (other than skin, intestine, testis and low grade) was similar to the incidence of gallium scan positivity in nodal non-Hodgkins lymphoma (*1,2,13*), and confirms that the gallium scan is able to detect extranodal lymphoma with approximately the same sensitivity as in nodal lymphoma. The stomach was the most commonly affected organ (85% gallium scan positive), and the oral/pharyngeal region was the most frequently affected region (87% gallium scan positive), but there were not enough patients in each of the various sites to permit statistical testing for differences in gallium scan positivity. The gallium scan was

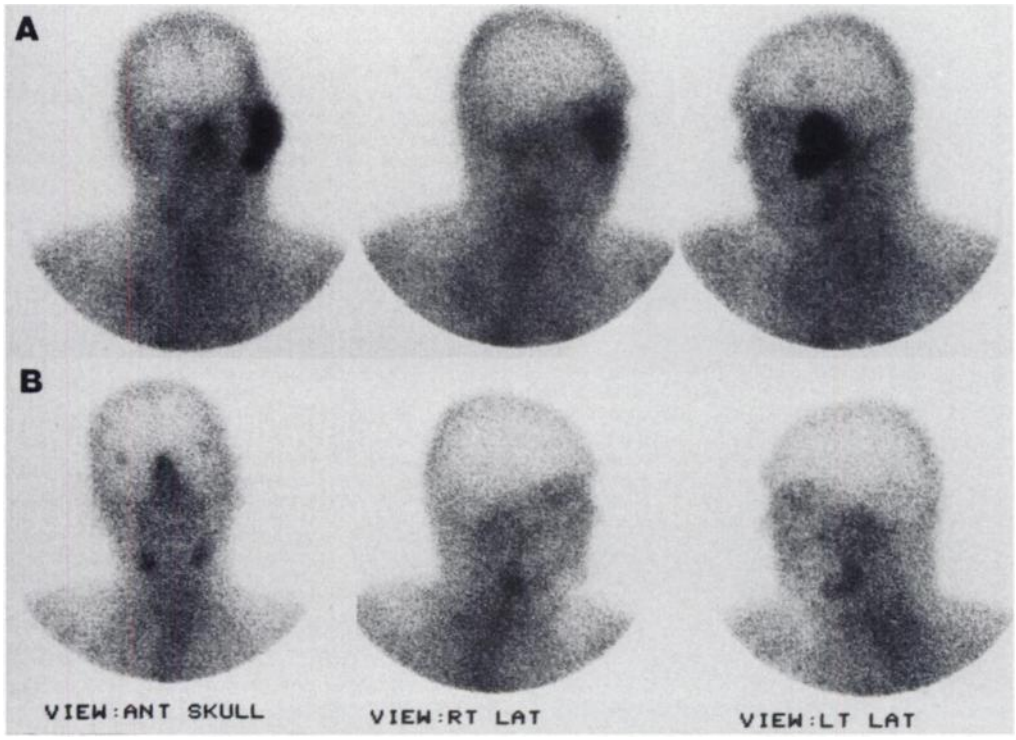

FIGURE 2. (A) Pretreatment and (B) post-treatment gallium scans showing complete resolution of abnormal uptake in the left parotid region.

usually positive at all sites except skin, intestine and testis where gallium scan positivity rates varied between 0% and 25%. This suggests the gallium scan is less useful in the staging of an extranodal lymphoma at these sites. Thallium has been shown to give more information in low-grade nodal non-Hodgkins lymphoma and may be more helpful in these cases (*1,16*). The gallium scan was significantly more likely to be positive with high and intermediate grades ($p = 0.015$), in agreement with the published literature (*1,16–18*), but this result should be interpreted with caution due to the small numbers in each group.

In approximately two thirds of patients (65%) there was good agreement between the gallium scan and the CT scan. In the remaining patients there were equal numbers in whom one modality was positive and the other negative. In these cases, clinical judgement was required to ensure that an abnormality detected by only one of these methods of assessment and not the other was indeed non-Hodgkins lymphoma and not just a spurious finding. These findings were similar to those of previous investigators who have shown that CT and gallium scans are complementary in investigating lymphoma (*1,2*). This study has shown the gallium scan to provide additional information in patient staging. In seven patients (8%) the stage of disease changed or they had treatment modification after the gallium scan. These were due to the detection on the gallium scan of sites of disease distant from the primary extranodal lymphoma that were not detected by other means. No correlation was demonstrated between prognosis and gallium scan positivity at the time of staging.

There were some limitations to our study. It was retrospective and most patients were treated in the last 5 yr so that the median survival time had only just been reached. Unlike the radiation oncology department, there was no usable database in the medical oncology department, so the proportion of patients in this study who were treated by radiotherapy alone was higher than might be expected if all patients presenting to the hospital were considered. However, 20 patients received chemotherapy alone and 21 received combined treatment, so the results were unlikely to be affected by the availability of databases. Although patients with gallium scan-positive lesions had the same survival rate as those with gallium scan-negative lesions, patients with gallium scan-positive lesions were more likely to have combined treatment, probably reflecting more advanced disease. It is, therefore, difficult to comment on the prognostic value of a positive gallium scan result before treatment in our patients. Some patients (23%) did not have a staging CT scan, including three in whom the gallium scan changed the stage of disease or treatment. The gallium scan did not include SPECT images, possibly underestimating the utility of the gallium scan because there are reports that suggest SPECT increases sensitivity (*19*). Our study had only 19 patients in whom the gallium scan was performed to assess response. This was not sufficient for any statistical analysis and the conclusion that the gallium scan was an accurate predictor of outcome could not be drawn. However, those in whom an initially positive gallium scan became negative appeared to have a relatively favorable results 86% were still alive when last seen. Although the value of the post-treatment gallium scan has been documented in nodal non-Hodgkins lymphoma (*1,3*), further studies are warranted to establish the usefulness of the gallium scan in the setting of the primary extranodal lymphomas.

CONCLUSION

The rate of gallium scan positivity varied widely between sites, and sites at which the gallium scan seems unlikely to be helpful were identified. In the majority of patients with extranodal lymphoma, a gallium scan positivity rate of 88% can be expected. Low-grade extranodal lymphomas had a low rate of gallium scan positivity and thallium scanning may be more useful in these patients. The gallium scan played an important role in staging these patients, leading to changes in the assigned stage or treatment in some cases. Patients whose positive pretreatment gallium scan became negative subsequently had a relatively favorable outcome.

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