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Malignant Lymphomas

# Persistent tumor $^{18}$F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma

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ABSTRACT

***Background and Objectives*. Early recognition of the ineffectiveness of chemotherapy could result in lower cumulative drug toxicity and tumor burden at the start of salvage therapy, which might improve clinical outcome. Therefore, we studied the value of $^{18}$F-FDG PET for early evaluation of response in patients with non-Hodgkin's lymphoma (NHL).**

***Design and Methods.* We studied 28 patients by $^{18}$F-FDG PET after a median of 3 cycles of polychemotherapy. The presence or absence of abnormal $^{18}$F-FDG uptake was correlated to clinical outcome (median follow-up: 17.5 months, range 4-47 months).**

***Results.* Five of 28 patients still had increased $^{18}$F-FDG uptake in one or more sites previously shown to be involved by lymphoma at baseline evaluation. Only one of these five patients entered complete remission (CR), whereas among the 23 patients with negative $^{18}$F-FDG PET studies, two died of toxicity during chemotherapy and all the others entered clinical CR ($p$<0.00001). All five patients with and 7/21 patients without residual abnormal $^{18}$F-FDG uptake relapsed or reprogressed (positive predictive value for relapse: 100%, negative predictive value: 67%). By Kaplan-Meier analysis, progression-free survival (PFS) at 1 and 2 years was respectively 20±18% and 0% for $^{18}$F-FDG PET positive patients and 81±9% and 62±12% for $^{18}$F-FDG PET negative patients ($p$=0.0001). Overall survival (OS) at 1 and 2 years was respectively 20±18% and 0% for $^{18}$F-FDG PET positive and 87±7% and 68±11% for $^{18}$F-FDG PET negative patients ($p$<0.0001).**

***Interpretation and Conclusions.* Persistent tumoral $^{18}$F-FDG uptake after a few cycles of polychemotherapy is predictive of CR, PFS and OS in NHL. Further studies are warranted to determine whether $^{18}$F-FDG PET has a predictive value independent from conventional prognostic factors. However, the sensitivity of qualitative $^{18}$F-FDG PET imaging in identifying patients with a poor outcome was insufficient. Earlier evaluation after only one cycle of chemotherapy and quantitative analysis might increase the sensitivity of 18F-FDG PET is predicting treatment failure.**


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Patients who respond more rapidly to chemotherapy could have a better and more durable response.[1] However, tumor volume reduction based on radiologic criteria is a late sign of effective therapy. Sometimes, an accurate definition of complete remission (CR) is difficult because residual masses observed at the end of induction chemotherapy may represent viable tumor or residual fibrosis.[2] Whole-body positron emission tomography (PET) using [$^{18}$F]-fluorodeoxyglucose ($^{18}$F-FDG) offers the possibility of differentiating sites of vital tumor from necrotic residual masses.[3] Malignant tissue is characterized by an enhanced rate of glycolysis in the presence of oxygen that results from amplification of the glucose transporter protein at the tumor cell surface as well as from increased activity of hexokinase.[4] Like glucose, FDG is transported into cells by a glucose transporter protein and rapidly converted into FDG-6-phosphate. As the latter is not a substrate for glucose-6-phosphate isomerase, it is biochemically trapped in metabolizing tissue.[5] If chemotherapy is effective, FDG uptake could be markedly diminished or even completely suppressed after a few cycles of polychemotherapy; this is well before tumor masses can be shown to be decreased by conventional imaging.[6] Therefore, we studied the value of $^{18}$F-FDG PET for early evaluation of response in patients with NHL. In particular, we examined the predictive value of such early evaluation for the clinical (CR) rate, progression-free survival (PFS) and overall survival (OS).

## Design and Methods

### *Patients*

Twenty-eight consecutive patients with histologically verified NHL who were scheduled to undergo chemotherapy were included prospectively between 5/94 and 3/97 in our study. The patients' characteristics are listed in Table 1. All patients gave fully informed oral consent.

### *Baseline evaluation*

Routine staging methods at diagnosis included at least clinical examination, laboratory screening, chest X-ray, computed tomography of chest and abdomen and bone marrow biopsy. Most patients (25/28)

**Table 1. Patient characteristics.**

| | |
|---|---|
| Number of cases | 28 |
| Age (years) (range 23-80 years) | 61 |
| Sex | |
| Male | 14 |
| Female | 14 |
| Histology (REAL Classification) | |
| Follicle center lymphoma, follicular, grade II | 3 |
| Follicle center lymphoma, follicular, grade III | 3 |
| Follicle center lymphoma, diffuse, small cell | 3 |
| Diffuse large B cell lymphoma | 16 |
| Peripheral T cell lymphoma, unspecified | 2 |
| Precursor T lymphoblastic lymphoma | 1 |
| Disease status | |
| Frontline therapy | 23 |
| First relapse | 3 |
| Transformed from low-grade lymphoma | 2 |
| Ann Arbor clinical stage | |
| Stage I | 4 |
| Stage II | 4 |
| Stage III | 5 |
| Stage IV | 15 |
| Treatment | |
| Anthracycline-based polychemotherapy | 23 |
| Mitoxantrone-based polychemotherapy | 2 |
| Cisplatin-based polychemotherapy | 3 |

**Table 2 : Sites of abnormal 18F-FDG uptake in 5 patients.**

1. Lung, pleura
2. Lymph nodes (mediastinal, retroperitoneal), bone (humerus)
3. Lymph nodes (abdominal mass)
4. Lymph nodes (mediastinal)
5. Lymph nodes (mediastinal), lung

were also evaluated by $^{18}$F-FDG PET at diagnosis; the other 3 were not because the PET scan was not available rapidly enough.

### *Early treatment evaluation*

Early evaluation by 18F-FDG PET was scheduled to be performed after 2-3 cycles of polychemotherapy. However, this was not possible in all of them for various reasons (infectious or other complications, technical reasons). Therefore, 11 patients were studied after 2 cycles, 10 after 3 cycles, 6 after 4 cycles and 1 after 5 cycles. Complete restaging with conventional imaging was not done at this time but $^{18}$F-FDG PET images were correlated with baseline clinical and CT examination. Comparison with baseline $^{18}$F-FDG PET was realized in all 25 available cases.

### *End of treatment evaluation*

One or two months after completion of therapy [median 6 (range 4-10) cycles of chemotherapy], all patients were re-evaluated by clinical examination and computed tomography with intravenous contrast enhancement to determine whether they had achieved CR. In the case of residual masses, a clinical CR was defined by stable masses during further follow-up of at least six months.

### *$^{18}$F-FDG PET studies*

Whole-body PET using $^{18}$F-FDG was performed with a Penn Pet 240-H Scanner (UGM, Philadelphia, PA, USA).Emission scans were recorded 45-90 min after intravenous administration of 200-300 MBq of $^{18}$F-FDG. All patients were asked to fast for at least 6 hours prior to the study. A whole-body acquisition was performed from the cervical to the inguinal region. This consisted of 10-12 separate overlapping acquisitions each covering 12.8 cm and performed over 4 minutes. Each subsequent acquisition was performed after a 6.4 cm displacement of the table. The total time of image acquisition was about 50 minutes. Images were reconstructed using filtered back projection with a Hanning filter and were reoriented in transverse, coronal and sagittal planes. A 4 mm voxel size was used. Isotropic 3D resolution was better than 8 mm. PET interpretation was performed in a qualitative manner without attenuation correction. All PET images were analyzed by a physician in the division of nuclear medicine and then reviewed by one investigator (GJ). Any focus of increased $^{18}$F-FDG uptake over background not located in areas of normal $^{18}$F-FDG uptake (central nervous system, heart, digestive tract, thyroid, muscles) and/or excretion (urinary tract) was considered positive for tumor. Furosemide (20 mg in slow intravenous injection) was administered in patients with suspected pelvic abnormalities to enhance $^{18}$F-FDG urinary elimination. These patients were studied later (60-90 minutes) and after voiding. Diazepam (5 mg) was given orally before $^{18}$F-FDG administration in most patients to prevent muscular uptake.

### *Statistical methods*

Comparison of groups for the probability of CR was performed with Yates' corrected chi-squared tests. OS and PFS were determined by standard Kaplan-Meier survival analysis, and comparison between groups was done by the log-rank test. All analyses were performed using Graphpad Prism 2.01 (Graphpad Software, San Diego, CA, USA).

## Results

Five of 28 patients still had increased 18F-FDG uptake in one or more sites previously shown to be involved by lymphoma at diagnosis (Table 2). Three of these 5 patients were studied after 2 cycles, one after 3 cycles and one after 5 cycles. One patient was studied at frontline therapy, two at first relapse and two at transformation from low-grade lymphoma. The patient in frontline treatment entered CR but relapsed 16 months after diagnosis and died a few weeks later. The other 4 patients never achieved CR, reprogressing 3, 3, 5 and 9 months after the start of polychemotherapy and dying 2, 2, 3 and 2 months later, respectively.

After a few courses of polychemotherapy $^{18}$F-FDG PET was negative in 23/28 patients. All patients

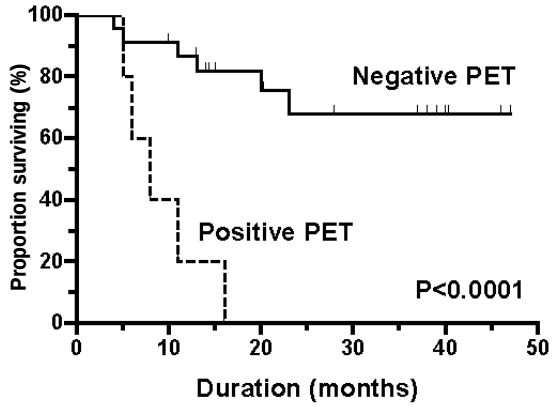


**Figure 1. Kaplan-Meier estimate of OS in 5 patients with positive 18F-FDG PET compared to 23 patients with negative 18F-FDG PET after 2-5 cycles of chemotherapy (p<0.0001)**

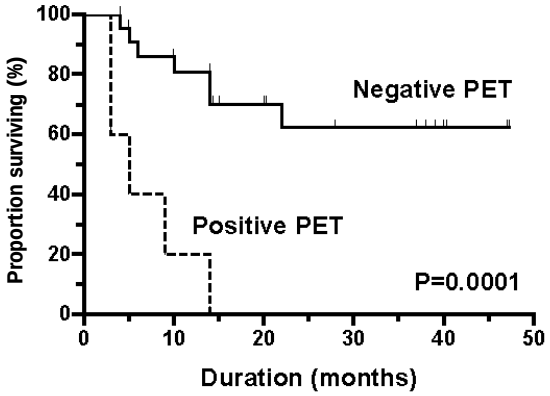


**Figure 2. Kaplan-Meier estimate of PFS in 5 patients with positive 18F-FDG PET compared to 23 patients with negative 18F-FDG PET after 2-5 cycles of chemotherapy (p=0.001).**

except one (in first relapse) were studied at frontline therapy. Two patients died of toxicity during chemotherapy. The other 21 patients entered clinical CR. Fourteen of these 21 patients remained in CR after a median follow-up of 28 months (range: 10-47 months) from diagnosis. Seven patients relapsed after a median follow-up of 10 months (range: 4-22 months). Five of these 7 patients died 11-23 months (median 15 months) after diagnosis and 2 are alive with disease 13 and 46 months after diagnosis.

The probability of achieving CR (20% vs 100%, $p$<0.00001) was significantly lower in patients with positive $^{18}$F-FDG PET after a few cycles of polychemotherapy. OS (20±18% vs 87±7% at 1 year, 0% vs 68±11% at 2 years, $p$<0.0001) (Figure 1) and PFS (20±18% vs 81±9% at 1 year, 0% vs 62±12% at 2 years, $p$=0.0001) (Figure 2) were also significantly different between the two groups. An example of a positive $^{18}$F-FDG PET study before and negative $^{18}$F-FDG PET study after 3 cycles of chemotherapy is illustrated in Figure 3.

## Discussion

Armitage *et al.*[1] have shown that CR, as assessed by plain films and computerized tomography scans, can be achieved in 70% of patients during the first 3 cycles of treatment. The length of time to reach CR was predictive of outcome. Sixty percent of those who did not achieve CR before cycle 5 of chemotherapy relapsed within 2 years. When CR was achieved after only 3 cycles, the relapse rate was only 20%. However, time to reach CR may be an imperfect indicator of the quality of response since the degree of tumor reduction differs between patients according to the size of initial masses, their site, histology and the type of treatment.[7] In addition, differentiation of tumor from fibrosis within residual radiographic masses is a problem in the differential diagnosis of residual disease in lymphoma.[2]

$^{67}$Ga imaging has been shown to be very useful in the monitoring of disease response or detection of recurrence in lymphoma. In a retrospective study, Kaplan *et al.*[8] reported that persistent $^{67}$Ga uptake after four to six cycles of combination chemotherapy for diffuse large cell lymphoma predicted a poor outcome. Patients with negative $^{67}$Ga scans had a 70% disease-free survival (DFS) at 3 years, whereas patients with positive scans had only a 24% DFS. Janicek *et al.*[9] prospectively evaluated 30 poor prognosis patients (bulky disease ≥ 10 cm, advanced stage aggressive NHL) with chest/abdominal/pelvic CT scans and $^{67}$Ga scans at baseline and following two cycles of therapy. After a median follow-up of 31 months, 94% of patients who had negative early restaging $^{67}$Ga scans (18/19 patients) remained free from progression, versus only 18% of those with positive scans (2/11). Preliminary results by Fayad *et al.*[10] indicated that a positive $^{67}$Ga scan after 2 cycles identified a subgroup of patients with aggressive NHL with poor outcome independently of tumor score. Three-year PFS and OS were respectively 53% and 65% for $^{67}$Ga-negative (n=70) and 29% and 40% for $^{67}$Ga-positive (n=31) patients. Preliminary results by Ben-Haim *et al.*[11] also showed that $^{67}$Ga scan after one course of chemotherapy reliably predicted response to therapy in lymphoma patients. Twenty of the 22 patients (91%) with a negative $^{67}$Ga scan and 12 of the 23 patients (52%) with a positive $^{67}$Ga scan achieved CR. Fourteen $^{67}$Ga-positive and 7 $^{67}$Ga-negative patients relapsed and DFS was significantly different.

Despite the important role of $^{67}$Ga in lymphoma imaging, $^{18}$F-FDG PET may be a more effective agent. $^{18}$F-FDG PET scanning is likely to be favored by clinicians and patients alike, because it allows same day imaging and because of the inherent superiority of PET imaging methods over standard gamma camera imaging in terms of sensitivity and spatial resolution. PET is also superior to conventional staging in this setting. Newman *et al.* showed in a pilot study includ-

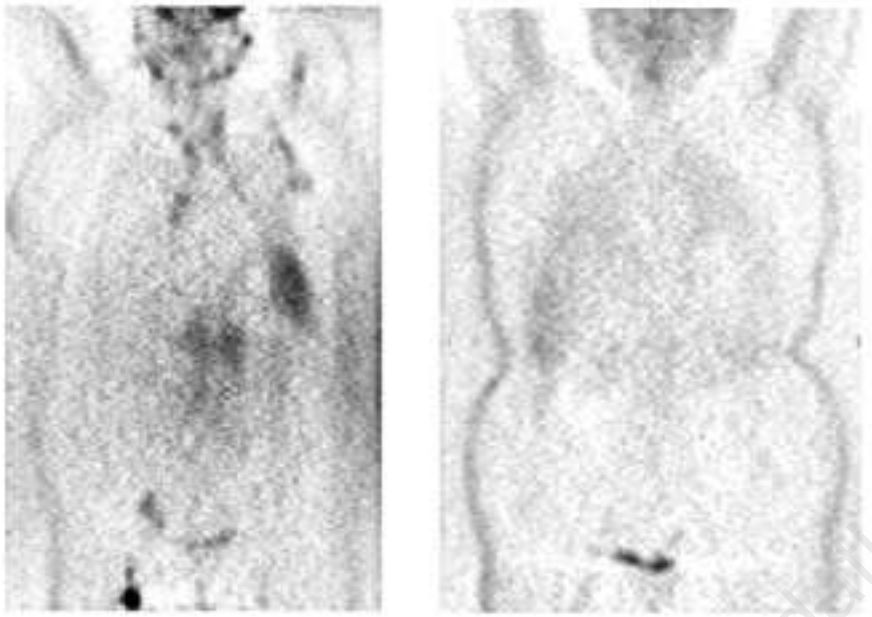

**Figure 3. $^{18}$F-FDG PET studies before and after chemotherapy in a case of high-grade NHL remaining in clinical CR after a follow-up of 40 months. On the left, many cervical, mediastinal and retroperitoneal lymph nodes as well as splenic infiltration can be seen at diagnosis. On the right, no residual abnormal $^{18}$F-FDG uptake was observed after 3 cycles of chemotherapy. Physiological uptake of $^{18}$F-FDG in the kidney and bladder was observed.**



ing 16 patients that $^{18}$F-FDG PET is more accurate than CT in the nodal staging of lymphoma patients.[12] A confirmatory study including 27 patients with Hodgkin's disease and 33 patients with NHL was reported by Moog *et al.*[13] PET showed lymphomatous involvement in 25 additional sites compared to those shown by CT (7 true positives, 2 false negatives, 16 unresolved). CT also showed some additional regions involved compared to those revealed by PET (3 false-positives, 3 unresolved). Staging was changed due to PET in 4 patients. $^{18}$F-FDG PET imaging may also provide more information than CT for the detection of extranodal lymphoma.[14] In addition, $^{18}$F-FDG PET could also detect bone marrow involvement not shown by bone marrow biopsy.[15,16]

Hoekstra *et al*.[17] compared results of early evaluation of response to treatment by $^{67}$Ga scintigraphy or by planar $^{18}$F-FDG scintigraphy with a conventional gamma-camera and a special collimator in 26 patients (13 with Hodgkin's disease (HD) and 13 with NHL). The scintigraphic appearance of involved sites was essentially the same with both tracers. In patients eventually achieving CR, tracer distribution had normalized after two courses; high uptake reflected treatment failure; faint uptake was associated with variable outcome. For investigation of residual masses and pre-treatment staging $^{67}$Ga was the preferred tracer because of higher contrast. However, in areas with considerable physiological $^{67}$Ga uptake, planar $^{18}$F-FDG scintigraphy could provide complementary information. Dimitrakopoulou-Strauss *et al.*[18] studied 10 patients with HD and NHL in relapse by $^{18}$F-FDG PET. They showed that a decrease in $^{18}$F-FDG uptake was associated with successful response to therapy, while progressive disease was correlated with increasing $^{18}$F-FDG uptake. Römer *et al.*[6] reported in their quantitative $^{18}$F-FDG PET study that standard chemotherapy of patients with NHL caused a rapid decrease of tumor $^{18}$F-FDG uptake as early as 7 days after treatment. The mean metabolic rates for $^{18}$F-FDG 7 days after initiation of chemotherapy was significantly lower in the 6 of 11 patients still in CR after a follow-up of 16±4 months. However, $^{18}$F-FDG uptake at 42 days was better than day 7 parameters in predicting long-term outcome.

Our study confirmed the prognostic value of early disease evaluation by $^{18}$F-FDG PET. The results in NHL patients showed that persistent tumor $^{18}$F-FDG uptake after 2-5 cycles of polychemotherapy was highly predictive of outcome, including the probability of achieving CR, PFS and OS. Only 1 of 5 patients entered CR but relapsed later. The positive predictive value of $^{18}$F-FDG PET after 2-5 cycles of polychemotherapy (defined as true positive by relapse and/or positive biopsy) was thus 100% (5/5) with no false positives. We did not attempt to correlate the results of positive $^{18}$F-FDG PET with conventional imaging techniques in this study. Early treatment evaluation by CT is disappointing because residual masses do not necessarily represent residual tumors.[3] We previously reported that $^{18}$F-FDG PET has higher diagnostic and prognostic value than classical CT scan imaging at the end of treatment evaluation in patients with HD or NHL. Zinzani *et al*. recently confirmed our findings in lymphoma patients with abdominal masses who have positive CT scans at restaging.[19] PET should be considered the noninvasive imaging modality of choice for differentiating early recurrences or residual disease from fibrosis. Pre-treatment $^{18}$F-FDG PET studies are useful to confirm that later residual $^{18}$F-FDG uptake is localized in areas involved by lymphoma at diagnosis. However, in routine clinical circumstances, the same information is already provided by the results of CT and clin-

ical examination at diagnosis. If residual $^{18}$F-FDG uptake is localized outside of known involved areas, inflammatory lesions must be excluded.

Qualitative $^{18}$F-FDG PET studies were not influenced by time between injection and imaging, as already reported in our previous study of NHL staging at diagnosis.[20] However, the time after injection is an important variable for quantitative PET studies. Significant differences in standard uptake values (SUV) might be found in a single tumor during a single scanning session depending on where in the body and, hence, when in the scanning sequence, the tumor is visualized.[21]

Our patient population was relatively heterogenous. We could not analyze patients treated by first line anthracyclin-based chemotherapy separately because only one of them had persisting $^{18}$F-FDG uptake. Most patients who had persistent $^{18}$F-FDG uptake were at high risk of treatment failure (2 patients in first relapse, 2 patients with transformed high-grade NHL). The true predictive value of $^{18}$F-FDG PET should be confirmed in a more homogenous patient population treated with the same chemotherapy regimen.

On the other hand, a negative $^{18}$F-FDG PET study after 2-4 cycles of chemotherapy confers a good probability of CR at the end of treatment (100% in our study). However relapses can still occur, even if $^{18}$F-FDG PET studies are negative. The negative predictive value (defined as true negative by the absence of relapse and/or negative biopsy of residual masses) was only 67% (14/21). Seven of 21 patients without residual abnormal $^{18}$F-FDG uptake relapsed or reprogressed. Thus, the sensitivity to identify poor outcome remains suboptimal. Earlier evaluation by $^{18}$F-FDG PET might be useful to recognize slower responders but this remains to be demonstrated. With our qualitative evaluation, low uptake is difficult to distinguish from background. Therefore, only quantification of $^{18}$F-FDG uptake with attenuation correction would allow more sensitive and earlier response evaluation than in our study. Major alterations of $^{18}$F-FDG uptake are easily recognized within days after starting chemotherapy and therapy-induced changes in $^{18}$F-FDG uptake might thus predict therapeutic efficacy.

Early identification of non-responders by $^{18}$F-FDG PET may lead in the future to a change from an unsuccessful therapy to a more effective one. Patients whose tumors remain $^{18}$F-FDG PET positive in the course of chemotherapy could be candidates for alternative treatment such as high-dose chemotherapy with autologous stem cell transplantation. However, only a large randomized trial will be able to determine whether such an approach could change the outcome of these patients.

In conclusion, our study demonstrates that persistent tumor $^{18}$F-FDG uptake after a few cycles of polychemotherapy is predictive of CR, PFS and OS in NHL. Most of the patients with persistent tumor $^{18}$F-FDG uptake did not achieve CR. A negative $^{18}$F-FDG PET study after 2-4 cycles of polychemotherapy confers a good probability of long-term survival but relapses can still occur. A positive $^{18}$F-FDG PET scan predicts lack of response rather than relapse. Earlier evaluation after only one cycle of chemotherapy and quantitative analysis might increase the sensitivity of $^{18}$F-FDG PET to predict relapse. Further studies are warranted to determine whether $^{18}$F-FDG PET has predictive value independently of conventional prognostic factors.

### Potential implications for clinical practice

- Early identification of non-responders to chemotherapy is possible by 18F-FDG PET
- A good probability of long-term survival is only observed in patients with negative 18F-FDG PET
- Relapses can still occur, even if 18F-FDG PET studies are negative.
- Further studies are warranted to determine whether 18F-FDG PET has predictive value independently of conventional prognostic factors.

### Contributions and Acknowledgments

*We declare that all authors participated actively in the design, execution, analysis and writing of the study. GJ, YB, MF Fassotte and GF were involved in the clinical diagnosis and treatment of patients and in the collection of clinical data. YB performed the statistical analysis.*

*FN, PP and PR were involved in all practical aspects of nuclear medicine from image acquisition to interpretation. All seven authors actively participated in correlating clinical and imaging data. They approved the content of the revised manuscript. They accepted the order of authorship. The order of authorship is related to the importance of their contribution to the analysis, writing up and revision of the manuscript.*

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### Disclosures

*Conflict of interest: none.*

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### Manuscript processing

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