Whole body amyloid deposition imaging by 123I-SAP scintigraphy

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Whole body amyloid deposition imaging by ^{123}I-SAP scintigraphy

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Abstract

Van Rheenen RWJ, Glaudemans AWJM, Hazenberg BPC. Whole body amyloid deposition imaging by ^{123}I-SAP scintigraphy

Amyloidosis is the name of a group of diseases characterized by extracellular deposition of amyloid fibrils. Deposition of amyloid can be localized or systemic. The ^{123}I-SAP-scan can be used to image extent and distribution of amyloid deposition in patients with systemic AA, AL and ATTR amyloidosis. Images are assessed in a semi-quantitative way by comparing each organ directly or indirectly to the normal blood-pool distribution. Considerable variation is observed between the findings on ^{123}I-SAP-scan and clinical manifestations of organ disease. Regardless, the ^{123}I-SAP-scan still provides both an impression of specific organ involvement as well as a global view of the amyloid load of the whole body. Due to physiological uptake of iodine degradation products in the stomach or to overwhelming uptake in an enlarged liver or enlarged spleen, visualization of abdominal organs nearby is not always easy and sometimes even impossible. In these cases SPECT (/CT) provides additional anatomical information to enable a more reliable assessment of such an organ.

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Introduction

Amyloidosis is the name of a group of diseases characterized by extracellular deposition of amyloid fibrils. This deposition can be localized (restricted to one organ or site of the body) or systemic (in various organs and tissues throughout the body). The clinical manifestations and diagnostic challenges will be described in another paper in this special issue.

Several types of amyloidosis can be identified by the type of protein involved. The three most important systemic types are: Amyloid A (AA) amyloidosis, immunoglobulin light chain-associated (AL) amyloidosis and transthyretin-associated (ATTR) amyloidosis. These types all have a different underlying pathology and clinical presentation. AA amyloidosis is associated with longstanding inflammatory disorders; its predominant clinical feature is nephropathy. In AL amyloidosis the underlying cause is a free light chains-producing monoclonal plasma cell dyscrasia; it has very diverse clinical manifestations. ATTR amyloidosis may be mutation-related (hereditary) or age-related (senile). The hereditary form is associated with mutations of the transthyretin (TTR) gene and its main manifestations are neuropathy and cardiomyopathy (1). The senile form is associated with non-mutated wild-type TTR and its main manifestation is a slowly progressive cardiomyopathy.

Histological proof remains the gold standard for the diagnosis of amyloidosis (2), but is sometimes difficult to obtain, is an invasive procedure and is subjected to sampling errors. Several diagnostic and laboratory tests are available to measure organ function indirectly. However, direct measurement of amyloid burden in the body is not available. Currently, the best whole body imaging method is the labelling of Serum amyloid P component (SAP) with radioactive ^{123}iodine (^{123}I-SAP). This nuclear imaging technique is used to image the extent and distribution of amyloid deposition in patients with all types of amyloidosis (3-7) and has nowadays an important role in the diagnosis and follow-up of patients with (suspected) amyloidosis.

This overview article highlights the different aspects of ^{123}I-SAP scintigraphy, from the tracer characteristics and the acquisition parameters to the interpretation, patterns, prognostic value and clinical relevance.

Tracer characteristics

In the human body SAP is produced only by hepatocytes, and the plasma concentration seems to be regulated at a rather constant level, even during deposition of SAP into amyloid. This indicates that the synthesis of SAP can be increased dramatically (4). The normal function of SAP is not known. All types of amyloid bind in a calcium-dependent manner to SAP, and therefore it is a suitable tool to be used for the imaging of all types of amyloidosis (8). Furthermore there does not seem to be such an interaction between SAP and normal tissue (9).

In healthy individuals SAP is mainly located in the plasma compartment, from which it is metabolized and excreted by the liver, with a half-life of about 24 hours (4). In patients with systemic amyloidosis the total amount of SAP associated with amyloid is many times higher than the total amount in the

plasma compartment of healthy individuals. During all phases of amyloid deposition and metabolism there is a constant exchange of SAP between the two compartments (figure 1) (10).

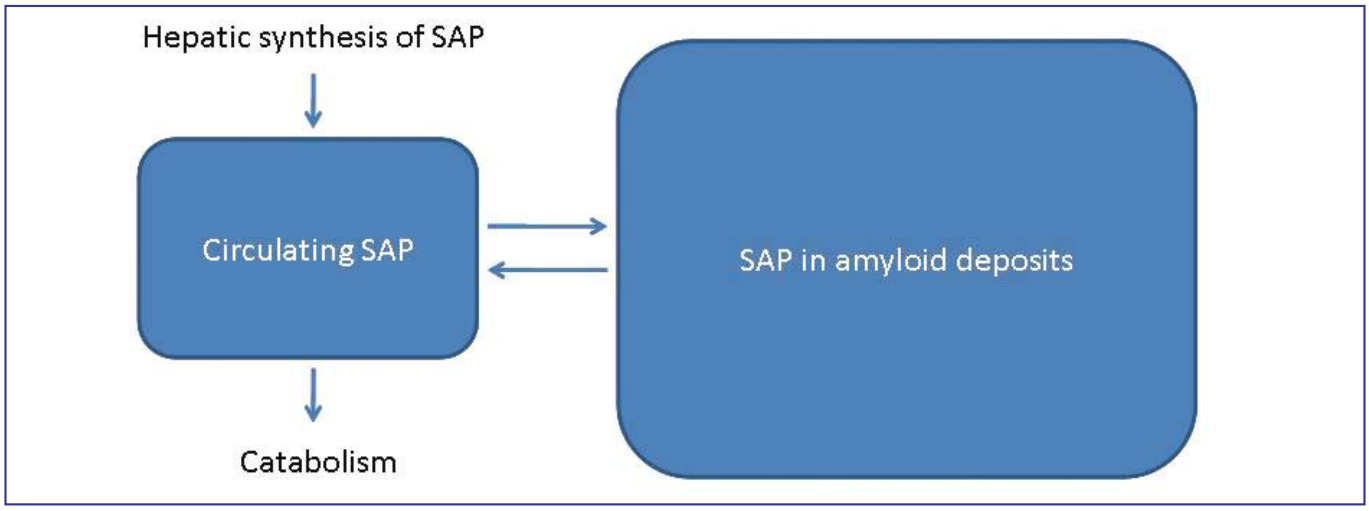

Figure 1. Schematic overview of biodistribution and metabolism of SAP in patients with systemic amyloidosis. Modified from reference 10

For the tracer production SAP has been isolated and purified from plasma of healthy donors. N-bromosuccinimide is used to oxidatively label the SAP protein with ^{123}I, while preserving its normal function (10). The molecule characteristics and the half-life of ^{123}I (13.2 hours) make it a very suitable radionuclide for amyloid imaging and, when labeled with high affinity to SAP, it is only metabolized in the liver. Radiolabeling methods and quality controls are performed as described (2).

Scintigraphy

Patients are intravenously injected with 200 MBq ^{123}I-SAP. Uptake of free ^{123}I in the thyroid is prevented by oral administration of potassium iodide. Scintigraphy is performed 24 hours after injection, with a dual head gamma-camera (Siemens MULTISPECT 2, Hoffman Estates, Illinois), equipped with a medium energy all-purpose collimator. Anterior and posterior total body images (in running mode;10cm/min) are acquired simultaneously, followed by detailed simultaneously acquired anterior and posterior images (10 min) of the abdomen and a single photon emission computed tomography (SPECT) of the abdomen. If necessary, a low-dose CT of the abdomen is performed additionally to obtain anatomic details.

Image assessment

The images are assessed in a semi-quantitative way by comparing each organ directly or indirectly to the normal blood-pool distribution (table 1). Organ involvement is graded

Organ	View	Visual assessment of abnormal uptake
Liver	Anterior	More than normal blood-pool in the heart.
Spleen	Posterior / SPECT	More than the liver. If liver is positive than similar uptake is abnormal.
Bone marrow	Posterior	Visible sacral bone, pelvis, long bones or individual vertebrae
Kidneys	Posterior / SPECT	More than vertebrae. If vertebrae are positive than similar uptake is abnormal.
Adrenal glands	Posterior / SPECT	One or both visible separate from kidneys, liver and spleen.
Joints	Anterior / Posterior	More than surrounding tissues.

Table 1. Semi-quantitative score of uptake: overwhelming (3+), intense (2+), positive without any doubt (1+), weak or doubtful (+) and normal (-). Modified from reference 12

3+ (overwhelming uptake), 2+ (intense uptake), 1+ (positive uptake without any doubt), ± (weak or doubtful) and – (normal) (11). Examples are shown in figure 2.

The following patterns may be observed and are typical for the different types of amyloidosis (12):

- AA Amyloidosis: abnormal uptake in the spleen is common. The three most frequent uptake patterns are: (1) abnormal uptake in the spleen only, (2) abnormal uptake in the spleen and kidneys, and (3) abnormal uptake in the spleen, kidneys and adrenal glands.
- AL Amyloidosis: abnormal uptake in the spleen is common. Uptake in other organs, such as liver, kidneys, bone marrow and joints, is very diverse.
- ATTR Amyloidosis: Only abnormal uptake in the spleen or kidneys is seen.

In healthy individuals there is no organ deposition of ^{123}I-SAP, and the tracer is then confined to the circulating blood pool and major blood organs (3, 13, 14).
Because of the semi-quantitative nature of the assessment, the inter-observer variety may be high, and therefore in our center the images are assessed by two experienced clinicians (rheumatologist and nuclear medicine physician) who will reach consensus.

Clinical correlation and prognostic value

Clinical studies with ^{123}I-SAP in patients with well-defined amyloidosis have shown a sensitivity of 100% in AA amyloidosis, 84% in AL amyloidosis and 95% in ATTR amyloidosis (10). The overall specificity is 93% (12). ^{123}I-SAP-scans can serve as a clinical tool for evaluation of amyloidosis patients. During life it is impossible to obtain a quantitative impression of the amount of amyloid in the body by using other procedures. Even multiple biopsies from many organs would only provide a qualitative impression of the amount of amyloidosis and serial monitoring of vital organs and tissues by biopsies is impossible (2). By using ^{123}I-SAP-

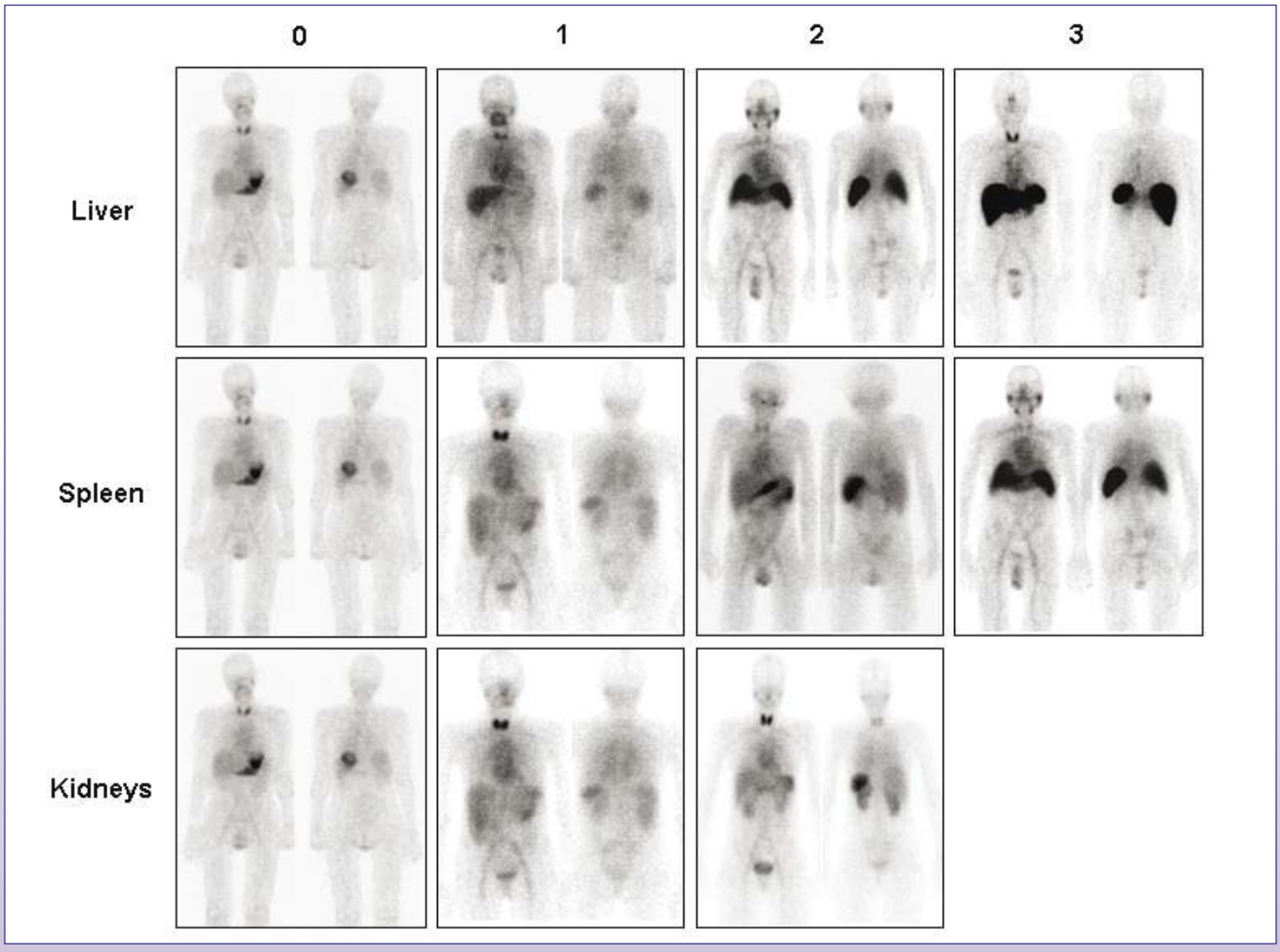

Figure 2. Clinical examples of semi-quantitative assessment of ^{123}I-SAP-scan. Grading of organ involvement: overwhelming (3), intense (2), positive without any doubt (1) and normal (0)

scans it has become possible to obtain a (semi-) quantitative assessment of the amyloid load of specific organs, as well as a general impression of the total body amyloid burden thereby providing a more complete staging of the disease and a non-invasive evaluation during and after therapy.

In clinical practice, however, the findings on a ^{123}I-SAP-scan and clinical manifestations of disease vary considerably among organs. Increased uptake of spleen and liver can be seen before clinical disease is present. On the other side, kidney involvement is detected earlier by proteinuria or loss of function than by ^{123}I-SAP-scintigraphy. Both heart and nerves are not visualized with this imaging method. Kidney uptake is concordant with severity of proteinuria (figure 3) and liver uptake in AL amyloidosis is concordant with increasing

Better Imaging; ^{123}I-SAP SPECT

Since the development of hybrid imaging systems, such as SPECT/CT, SPECT and CT images of the abdomen have been added to our routine imaging protocol of ^{123}I-SAP. This obviously has substantial advantages.
On planar imaging physiological stomach uptake and an enlarged liver can obscure the visualisation of the spleen. At the same time the spleen (and an enlarged liver) can obscure visualisation of the kidneys and adrenal glands (1). Inaccurate information about organ involvement may have a negative effect on diagnosis, disease staging and follow-up of a patient with amyloidosis (1). Empirically it has been proposed that SPECT imaging should solve the problem of obscured visualisation of abdominal organs on a SAP scan. However,

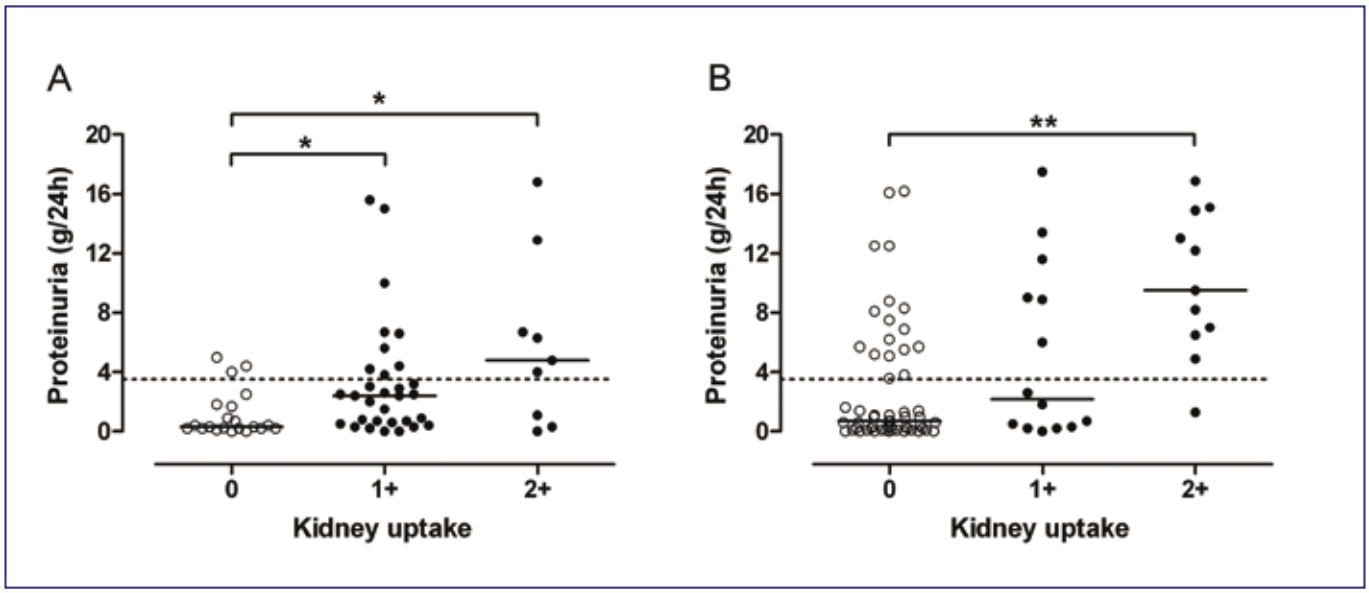

Figure 3. Proteinuria and ^{123}I-SAP kidney uptake. The dashed line indicates heavy proteinuria (>3.5 g/24h). Horizontal lines show median values. (A) AA patients. (B) AL patients. Reproduced with permission from reference 12.

worst prognosis from patients in whom chemotherapy still may be beneficial (figure 4).
Furthermore uptake within the joints can be challenging in the assessment of a scan because of the false positive outcome in patients with arthritis, such as rheumatoid arthritis. Uptake of SAP in these cases is non-specific because of synovial effusion in arthritic joints due to the increased blood-pool at these sites.
As already stated above, the ^{123}I-SAP-scan is not suitable for the evaluation of the heart, most likely due to lack of fenestrated endothelium in the myocardium (12). To determine amyloid burden of the heart, an indirect imaging method is available that measures the innervation of the heart (^{123}I-MIBG). Further on, due to not crossing the blood-brain-barrier, ^{123}I-SAP is not able to visualize amyloid plaques in the brain. In this situation imaging with ^{11}C-PiB comes into sight. These two radionuclides are described elsewhere in this special issue.

this issue has not yet been studied.
In our practice SPECT/CT has become a complementary modality next to the static planar images. Often physiological uptake in the stomach hinders accurate assessment of the spleen, but with SPECT/CT this problem can be addressed easily (figure 5). With regards to the adrenal glands it seems that SPECT/CT is the best way to assess involvement by giving accurate grading (figure 6). SPECT/CT of the abdomen is now routinely used in these patient groups and a patient study of the additional value of SPECT and CT has just been finished.

Conclusion

The ^{123}I-SAP-scan is a non-invasive sensitive imaging modality to detect and grade amyloid deposits in most organs (except heart and brain) in patients with all types of

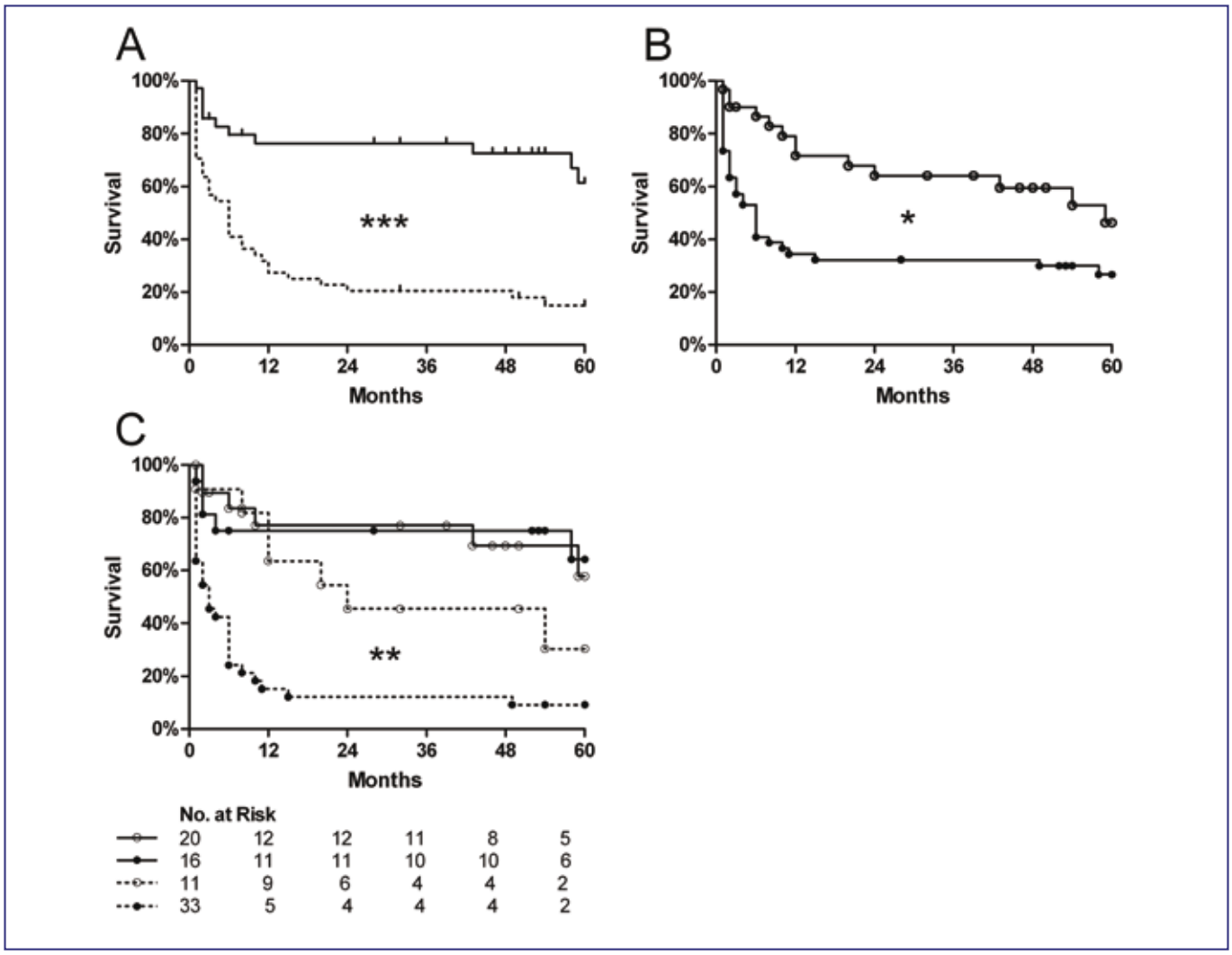

Figure 4. Survival of 80 patients with AL amyloidosis. (A) Patients with (dotted line) and without (solid line) clinical involvement of the heart. (B) Patients with high (>50%) (●) and low (<50%) ( ) tissue retention of SAP after 24 hours (EVR_{24}). (C) Patients stratified according to high (>50%) (●) and low (<50%) ( ) EVR_{24} and presence (dotted line) or absence (solid line) of clinical involvement of the heart. Reproduced with permission from reference 11

amyloidosis. Although there is a high variety among individual patients, its use for diagnosis, disease staging and follow-up in patients with amyloidosis makes it a valuable tool in the clinical management of patients with amyloidosis. The semi-quantitative assessment and sometimes obscured nearby abdominal organs by overlap can make accurate and consistent assessment difficult and sometimes impossible. However, this problem can be addressed by collaborative assessment and the use of SPECT/CT imaging.

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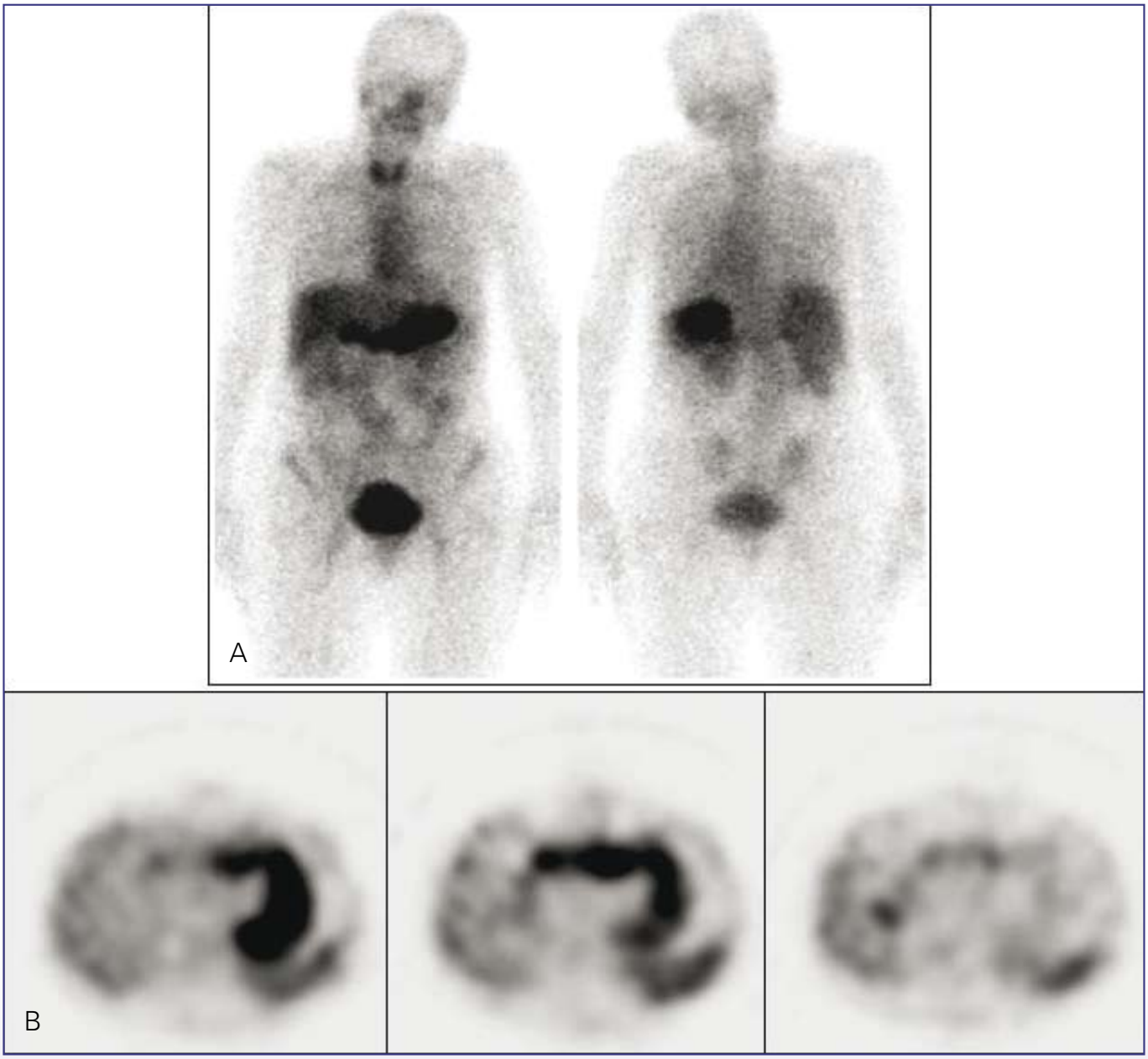

Figure 5. (A) Planar SAP scan image (anterior / posterior) of a patient with AA Amyloidosis; the spleen is difficult to assess because of uptake in the stomach. (B) SPECT/CT images conclusively show physiological uptake in the stomach and positive uptake (1+) in the spleen.

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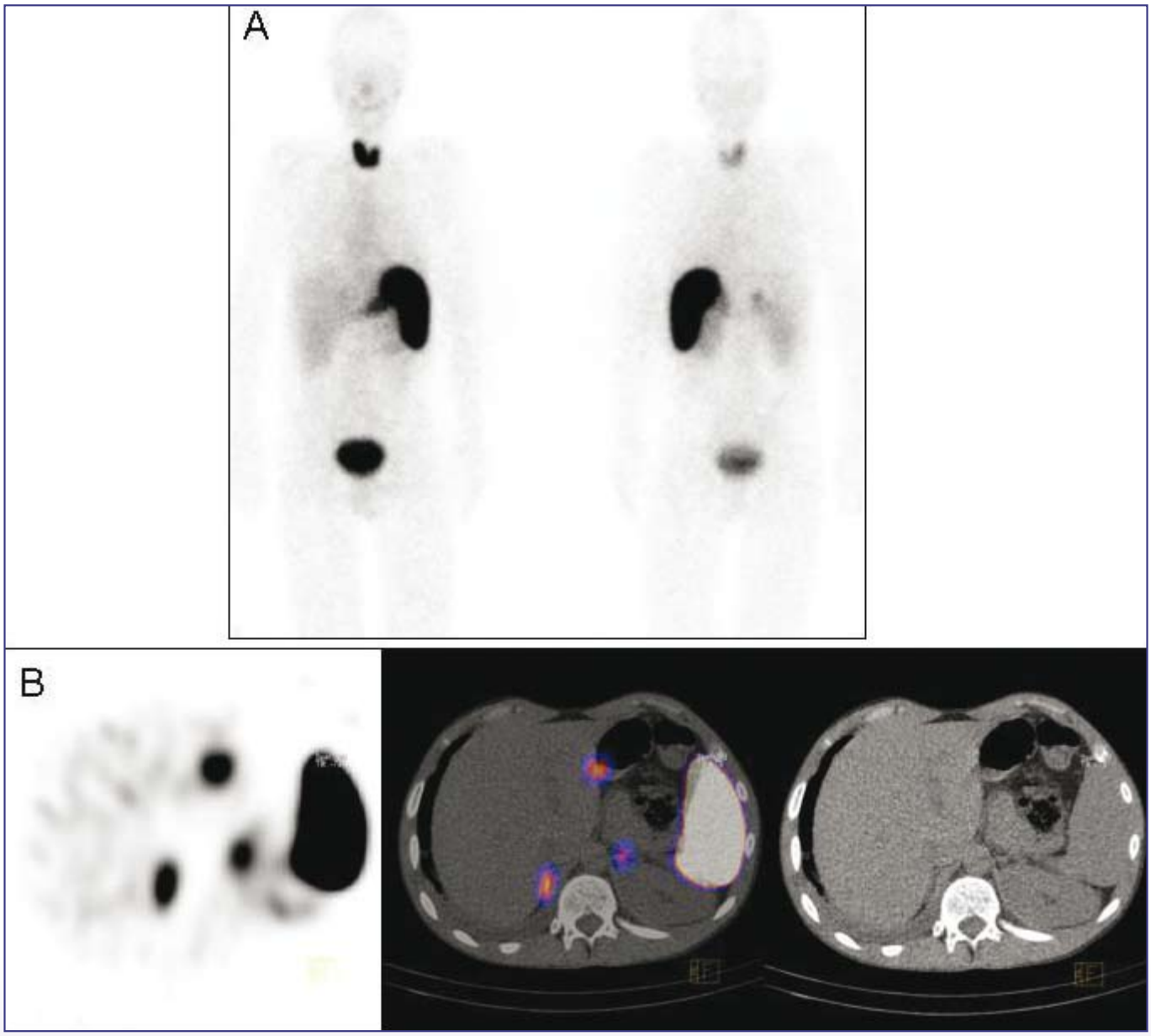

Figure 6. (A) Planar SAP scan image (anterior / posterior) of a patient with AA amyloidosis. The adrenal glands are difficult to assess. (B) SPECT/CT images show uptake in both adrenal glands

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