



MRI Measurement of Liver Iron Concentration

Case Study Collection

Iron Overload Monitoring and Management



June 2017

Resonance
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The Resonance Health logo consists of the word "Resonance" in a dark blue, bold, sans-serif font above the word "Health" in a green, bold, sans-serif font. Between the two words is a graphic element: a green circle containing a stylized cluster of dark blue circles, connected by a thin green line that curves upwards and to the right, ending near the "H" in "Health". Below the "Health" text is the tagline "Be Better Informed" in a smaller, lighter green font.



MRI Measurement of Liver Iron Concentration

News Release, U.S. Food and Drug Administration, FDA approve FerriScan as first imaging companion diagnostic for chelation therapy with Exjade® (Deferasirox), Jan 2013

"The FDA reviewed data for the FerriScan through the de novo classification process. The FDA's granting of the de novo request for FerriScan was based largely on data from the Exjade clinical studies that used FerriScan LIC results as the primary outcome measure. Additionally, investigators conducted a 230-patient study that found FerriScan results were as accurate as liver biopsy for measuring LIC."

"The FerriScan device is a non-invasive test that helps physicians to select appropriate patients for Exjade therapy as well as monitor their response to the drug, and discontinue therapy when LIC reaches safe levels."

UK Forum on Haemoglobin Disorders, *Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK*, 2016

"Liver Iron Concentration LIC should be assessed using a validated and standardised MR technique. R2 (FerriScan) is preferable to R2* because the methodology is more robustly standardised and has been licensed for use in routine clinical practice."

"MRI LIC methods should not be used interchangeably. In particular, sequential MRI estimations in an individual patient should be done with the same methodology."

Association of the Scientific Medical Societies in Germany, *Guideline for diagnosis and treatment of secondary iron overload in patients with congenital anemias*, 2015

US Department of Health and Human Services, *Evidence-based Management of Sickle Cell Disease, Expert Panel Review*, 2014

Thalassaemia International Federation, *Guidelines for the Management of Transfusion Dependent Thalassaemia*, 3rd Edition, 2014

The Fred Hutchinson Cancer Research Center and Seattle Cancer Care Alliance, *Long-term follow-up after hematopoietic stem cell transplant general guidelines for referring physicians*, 2014



The Northern California Comprehensive Thalassemia Network and Children's Hospital, Oakland, *Thalassemia Standards of Care Guideline*, 2012

The Cooley's Anemia Foundation (USA), *2012 Position Statement*

University Health Network and Toronto General Hospital, Canada, *2012 Guidelines for the Care of Patients in the UHN Red Blood Cells Disorders Program*

Australian guidelines for the assessment of iron overload and iron chelation in transfusion-dependent thalassaemia major, sickle cell disease and other congenital anaemias, 2011

FerriScan Testimonials

"Having a technique that is standardised and validated means that you have an accurate result, no matter whether at different time points, done in different machines, or in different places. FerriScan results are very accurate, reproducible and you can trust them to guide the treatment of your patients and know that their health outcomes are going to be optimal if you target your treatment accurately."

Dr Josu de la Fuente, Consultant Paediatric Haematologist and Senior Lecturer,
Imperial College London and Director of the Paediatric Blood and Marrow Transplant Programme

"Cancer survivors with excess iron may be exposed to this iron for years ahead if untreated, so timely monitoring and reduction of iron burden is an important goal. In our recent data we found even at relatively low thresholds of serum ferritin, liver iron concentration can be elevated in these patients. Conversely, a high serum ferritin, which may be caused by inflammation or other factors, may not be reflective of high liver iron concentration. FerriScan provides us with a standardized and reliable tool to screen cancer survivors and guide treatment where required. FerriScan is especially suitable for pediatrics as it is free-breathing and quick. It is also unaffected by the presence of fat in the liver, which can be an issue in cancer survivors as a result of their therapy. We recommend that all patients who have undergone hematopoietic stem cell transplantation (HSCT) or those who have received > 10 transfusions should be considered for assessment using FerriScan."

Dr Angela Smith, Assistant Professor,
Division of Pediatric Blood and Marrow Transplantation at the University of Minnesota

"On behalf of the Board of Directors of Thalassaemia International Federation (TIF) I hereby express our sincere congratulations to Resonance Health Ltd for the achievement of providing 30,000 FerriScans worldwide, supporting in this way the global effort of our Federation to best practice iron load monitoring in patients with haemoglobin disorders.... Through the measurements it has been possible to compare with other less validated technologies and identify differences which placed patients at risk..."

Panos Englezos, President, Thalasaemia International Federation (TIF)

"I can honestly say that I'm not sure where we would be without FerriScan and the wonderful team at St Mary's. Christie (my daughter) was diagnosed at 12 weeks old and has had regular blood transfusions as part of her care. She needed accurate quantitative monitoring of her liver iron levels. Blood tests and standard MRI liver assessments elsewhere did not provide accurate information and it was only when she had a FerriScan MRI with the reliable quantitative measurement that we discovered she had significant iron overload in her liver and Doctors were able to optimise her treatment. I would like to see all patients with Diamond Blackfan Anaemia who are at risk from iron overload have access to the optimal FerriScan technology, and expertise that matches the team at St Mary's."

Leisa Batkin, Chair, Diamond Blackfan Anaemia Society

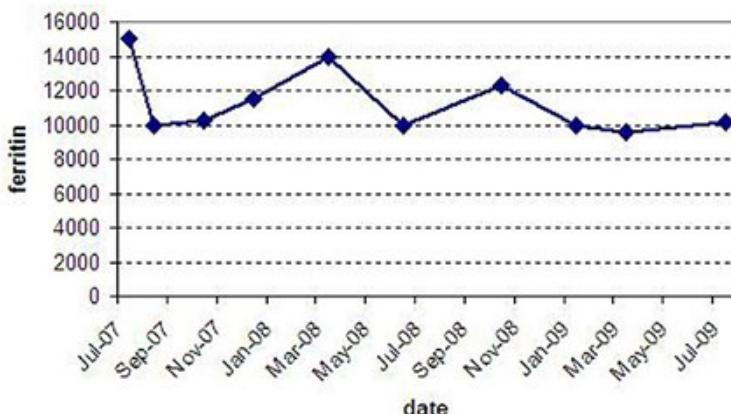
"We aim to incorporate the very best diagnostics into care pathways for haemoglobinopathy patients and those at risk of iron overload. The introduction of FerriScan has significantly improved health outcomes and the excellent collaboration with Resonance Health to provide 1000 patients with access to optimised monitoring is certainly something to be celebrated."

Dr Alavi, Consultant Paediatric Radiologist, St Mary's

Christie Batkin (7) is one of over 1000 patients benefitting from FerriScan at St Mary's Hospital, pictured with Melanie Baxter, Resonance Health and Dr Alavi, Consultant Paediatric Radiologist.



A 26 year old male with beta- thalassaemia major who was diagnosed with rheumatoid arthritis at the age of 15 had a persistently high serum ferritin value of above 10,000 µg/L despite regular chelation therapy using Deferiprone 7 days a week.



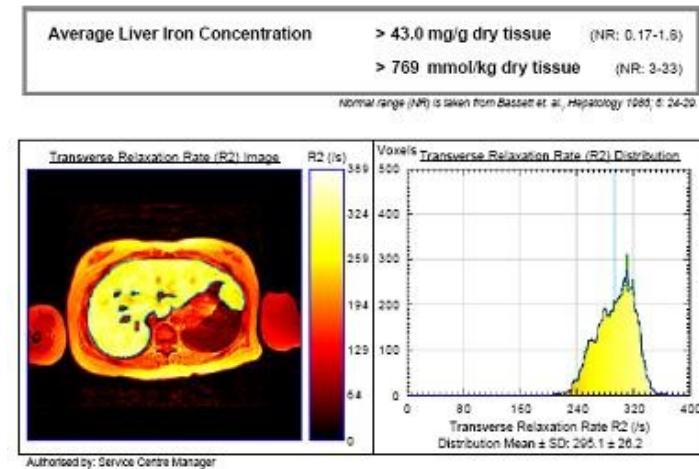
The patient's renal function was normal and the review of liver enzymes supported this with an average ALT of 65 IU/L (normal range 0-31 IU/L). The patient was previously treated for Hepatitis C with Interferon and Ribavarin during 2006/07. The patient's viral load is now negative.

Several MRI scans had been obtained in the past using the T2* technique. The results were as follows:

	CMR 2003	CMR 2007
Liver Iron	6.8 mg/g/dw	7.1 mg/g/dw
Cardiac T2*	34.5 ms	54.2 ms

On the basis of these results, mild changes were made in the chelation therapy with a view to optimise the iron load in the liver. A low dose of Desferrioxamine was added to the treatment twice a week. It was felt that the raised serum ferritin value was due to an acute phase response due to the rheumatoid arthritis. A normal result was obtained in the most recent glucose tolerance test.

In 2009, FerriScan was performed as part of the routine monitoring:



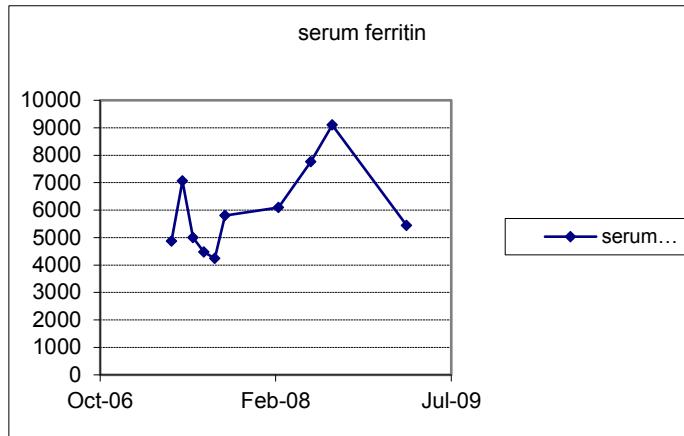
Based on the FerriScan result, the chelation therapy was intensified by increasing the Desferrioxamine dosage to 40 mg/kg/day 5 days a week in conjunction with Deferiprone administered seven days a week. Another FerriScan will be performed in 6 months time. If the liver iron is not decreasing satisfactorily, a port-o-cath for intravenous Desferrioxamine may be considered.

This case study demonstrates the differences in severity of iron burden using different modalities to assess liver iron and the impact this can have on chelation therapy.

Thalassaemia Major Case Study

A 37 year old patient with beta thalassaemia major had a persistently high serum ferritin value despite reporting good compliance to treatment. Optimal doses of chelation were failing to reduce serum ferritin values.

Investigations showed a serum ferritin value of 6093 µg/L. A review of the serial serum ferritin was undertaken and showed persistently stable but high values.



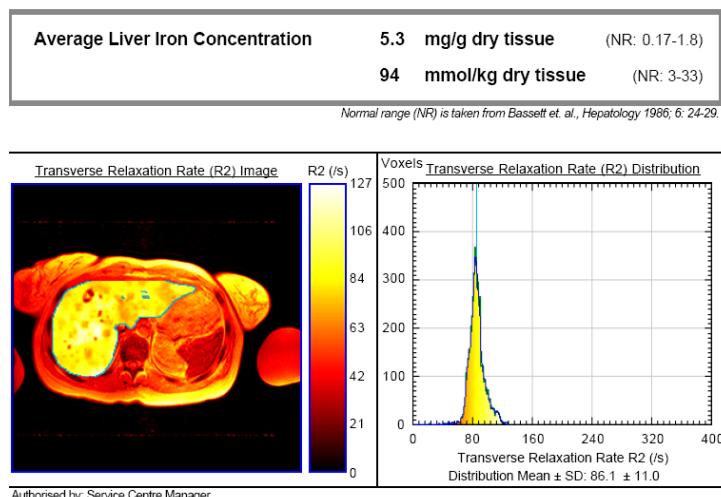
The patient had normal renal function, liver function ALP 97 IU/L, ALT 43 IU/L, Bilirubin 9 µmol/L.

An MRI scan looking at myocardial iron loading showed the following:

Cardiac T2*	21.5 ms
Liver T2*	6.1 ms (Liver Iron 2.1mg/g/dw)
Ejection Fraction	67%

Serum ferritin was not reflective of the iron burden. ESR was 22 mm/hr and CRP was 9. RF and ANA all negative.

A FerriScan was performed due to concerns regarding the serum ferritin. The result showed a liver iron concentration of 5.3 mg/g/dw.



As a result, the patient was advised to continue on current iron chelation regime at the existing doses. The plan is to re-scan the patient with FerriScan if there is a persistent and steady increase in the serum ferritin value above 8000 µg/L.

This case highlights that serum ferritin can be unreliable in accurately assessing the severity of the iron load. The use of FerriScan in accurately confirming the severity was very important in this case as the patient could have been over chelated.

A 22-year old male with β thalassaemia dependent on blood transfusion 3 to 4 weekly ever since the age of 4 months.

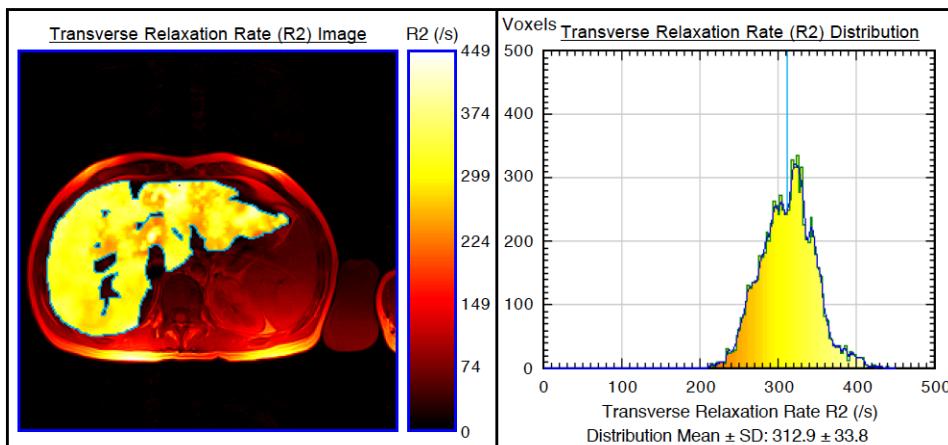
Iron chelation therapy consisted initially of subcutaneous (SC) Desferrioxamine (DFO) 5 nights per week but adherence with DFO chelation therapy may not be optimal, ferritin levels remain high at 1,000 to 2,000 ng/mL between 1999 and 2006.

In 2006 at the age of 18 years, he complained of intermittent palpitations; a 24 hour tape showed atrial fibrillation. A transthoracic echocardiogram was entirely normal with negative adenosine challenge. Cardio-toxicity due to iron overload was suspected but he failed to turn up repeatedly for three cardiac MRI appointments. From 2006 serum ferritin levels remain consistently above 2,000 ng/mL and iron chelation therapy was switched over to Deferasirox (DFX) at 30 mg/kg daily in 2006/2007. The patient then relocated to another town and was seen intermittently in the local hospital. He re-presented to King's College Hospital in April 2010 with palpitations.

FerriScan R2 MRI in April 2010 showed he had severe iron overload:

Average Liver Iron Concentration	> 43.0 mg/g dry tissue (NR: 0.17-1.8)
	> 770 mmol/kg dry tissue (NR: 3-33)

Normal range (NR) is taken from Bassett et al., Hepatology 1986; 6: 24-29.



Authorised by: Service Centre Manager

Cardiac T2* was 4.2 msec.

Intensive continuous IV DFO at 50 mg/kg per 24 hours was started. Sub-optimal blood transfusion probably contributed to mild hypersplenism (steady WBC 3.0-3.5 and neutrophils 1.00-180 x 109/L, and platelets 90-120 x 109/L).

As symptoms of palpitations improved, and due to difficulty in maintaining continuous IV access, DFO was switched to continuous subcutaneous delivery and Deferiprone (DFP) at 75 mg/kg/d was added to iron chelation therapy.

FerriScan with cardiac T2* will be performed as part of routine monitoring of response to iron chelation therapy.

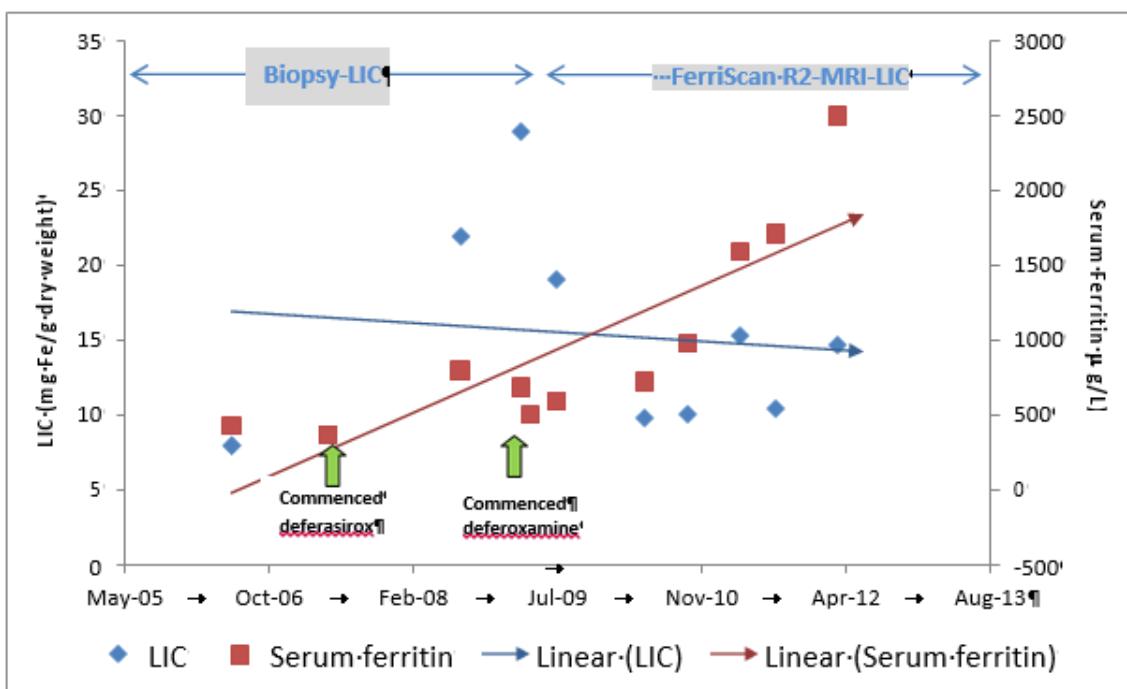
Thalassaemia Intermedia Case Study

A patient with β -thalassemia intermedia began chronic blood transfusions at age seven years, in March 2006. In June 2006, he underwent liver biopsy, with a liver iron concentration (LIC) measurement of 7.9 mg Fe/g dw. The patient's serum ferritin was 430 μ g/L. In March 2007, he commenced chelation therapy, using deferasirox. At this time, the serum ferritin measured 372 μ g/L.

In August 2008, an LIC measurement obtained by liver biopsy was 22mg Fe/g dw and serum ferritin value was 800 μ g/L. A subsequent liver biopsy in March 2009 showed an increase in LIC to 28.9 mg Fe/g dw, while his serum ferritin had fallen to 687 μ g/L.

In April 2009, the patient's medication was changed to deferoxamine and his serum ferritin measured 504 μ g/L. In July 2009, the patient underwent a FerriScan R2-MRI and his LIC was measured 19 mg Fe/g dw, while serum ferritin measured only 594 μ g/L.

Subsequent FerriScan LIC measures indicated that the patient's serum ferritin measurements were not indicative of the iron burden.



Cause of lethargy – Iron overload – Confirmed by MRI

1. History and examination

A 39 year old Caucasian man presented with lethargy and fleeting aches in the small joints of the hands. Physical examination was completely normal.

2. Investigations for diagnosis

Full blood picture, ESR, LFTs were normal. Serum transferrin saturation (TS) was 85% and ferritin (SF) levels 890 (g/L). Testing for the C282Y and H63D mutations in the haemochromatosis (HFE) gene were negative. Patient referred for quantitative measurement of liver iron concentration (LIC) using non-invasive MRI (FerriScan®). Hepatic iron concentration was elevated: 90 mmol/kg dry tissue (NR: 3-33^[1]).

3. Diagnosis

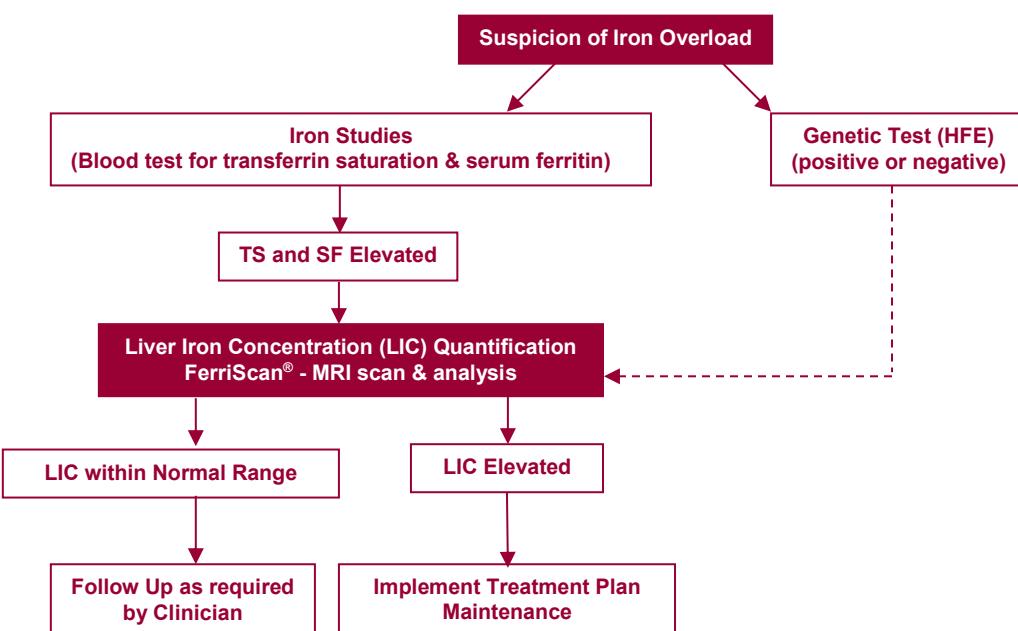
Iron overload (haemochromatosis – not HFE related), confirmed by increased liver iron concentration.

4. Management

Refer patient for phlebotomy therapy. FerriScan used to monitor LIC.

5. Discussion

- The most common symptoms associated with iron overload in adults include unexplained fatigue, malaise and arthralgia^[2,3]
- Elevated transferrin saturation and ferritin levels suggest body iron accumulation^[3]
- Although testing for C282Y and H63D mutations in the HFE gene were negative, this does not completely rule out genetic hemochromatosis^[2]
- Measuring LIC using non-invasive MRI (FerriScan) assists in the diagnosis of iron overload. The outcome from quantitative LIC will also assist in monitoring treatment in the early stages^[4]



[1] Normal range (NR) is taken from Bassett et. al., Hepatology 1986; 6: 24-29.

[2] Pietrangelo, A. **Heredity Hemochromatosis – A New Look at an Old Disease**. The New England Journal of Medicine, 2004; 350:2383-2392.

[3] Dooley, J. & Worwood, M. **Guidelines on diagnosis and therapy: Genetic Haemochromatosis**. British Committee for Standards in Haematology. 2000. Abingdon, Oxford, Darwin Medical Communications Ltd. Available: www.bsghguidelines.com.

[4] St. Pierre, T.G., Clark, P.R., Chua-anusorn, et al. **Non-invasive measurement and imaging of liver iron concentrations using proton magnetic resonance**. Blood, 2005; 105:855-861. Available: www.bloodjournal.org/cgi/content/abstract/105/2/855

Sickle Cell Anaemia Case Study

A 42 year old female patient diagnosed with sickle cell anaemia had complicated recurrent hospital admissions with vaso-occlusive crises and chest syndrome.

Her serum ferritin level was persistently above 3000 µg/L. The patient was previously transfused as a child and also during hospital admissions abroad. She was not on any long-term transfusion program and therefore it was difficult to accurately assess the total cumulative transfusion history.

The liver enzymes were unstable and steadily worsening. The serum ALT was 118 IU/L and persistently elevated.

In addition, there was a recent onset of diabetes and the assumption that she had started her menopause as she had not had a period for 5 months.

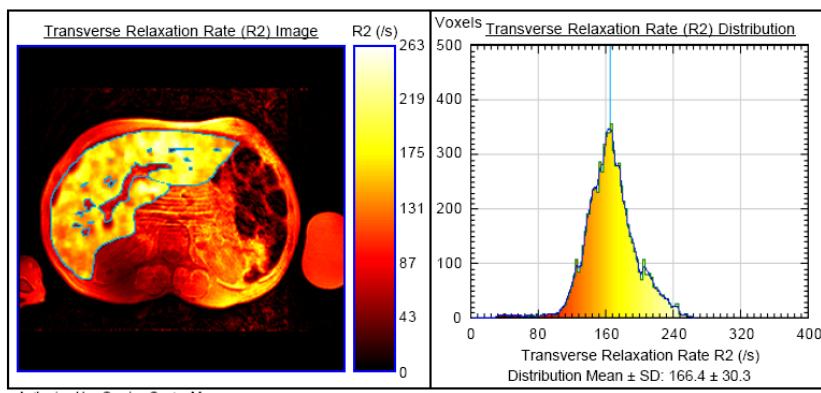
The pathology results were:

FSH	1 IU/L
LH	0.5 IU/L
Oestradiol	< 100 pmol/L

These findings were in keeping with hypogonadotropic hypogonadism rather than a true menopause. The outcome prompted an assessment of the patient's liver iron concentration using FerriScan:

Average Liver Iron Concentration	15.8 mg/g dry tissue (NR: 0.17-1.8)
	283 mmol/kg dry tissue (NR: 3-33)

Normal range (NR) is taken from Bassett et. al., Hepatology 1986; 6: 24-29.



Authorised by: Service Centre Manager

The FerriScan R2-MRI analysis confirmed a high liver iron concentration and the patient was placed onto regular chelation therapy.

This case confirmed that the persistently raised serum ferritin level was reflective of a high liver iron burden and the hypogonadotropic hypogonadism was probably related to the iron overload.

A 45 year old lady with sickle cell disease has been treated with intermittent and regular transfusions over the past 25 years.

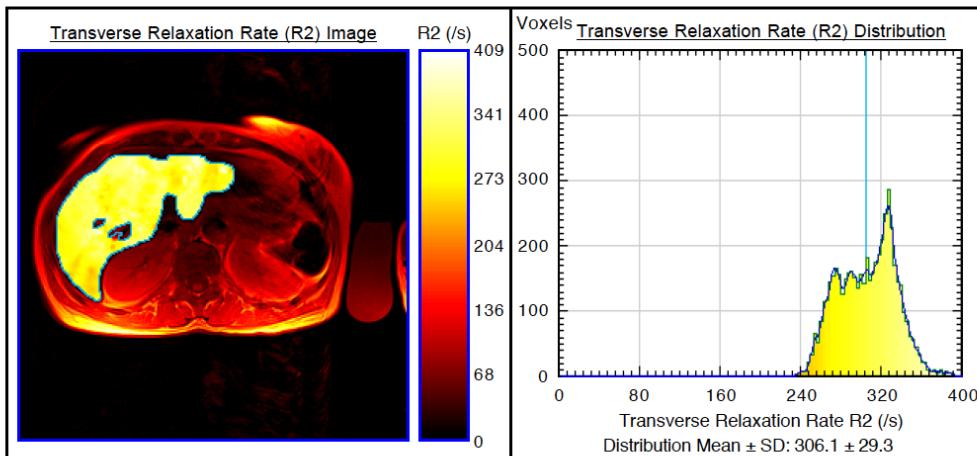
She has developed multiple complications from her sickle cell disease including bilateral non-proliferative retinopathy, avascular necrosis of right hip and left shoulder (requiring replacement) and multiple acute chest syndromes (May 1998, December 1999, May 2008 and November 2008).

Between 1985 and 1991 she was placed on a transfusion programme of 2-3 units every 3-4 weeks for prevention of acute pain. Between 1988 and 1995 she received iron chelation treatment with subcutaneous desferrioxamine which she was apparently compliant with. However her serum ferritin on transfer to King's College Hospital was raised at 4836 ng/ml. From January 1992 to December 2009 she received 169 units of blood as intermittent transfusions during acute admissions. 104 units were "top-up" and 65 were exchange (mainly manual).

From 1992 her serum ferritin remained raised above 2000 ng/ml. In November 2009 an R2 MRI was performed.

Average Liver Iron Concentration	> 43.0 mg/g dry tissue	(NR: 0.17-1.8)
	> 769 mmol/kg dry tissue	(NR: 3-33)

Normal range (NR) is taken from Bassett et. al., Hepatology 1986; 6: 24-29.



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This showed severe iron overload. A cardiac T2* carried out at the same time was 32.8ms (normal). Serum ferritin at this time was 3144 ng/ml. She was commenced on Deferasirox at 20mg/kg/day which increased to 30mg/kg/day in September 2010. Her most recent ferritin is 2597 ng/ml and she will have a reassessment FerriScan with cardiac T2* in February 2011.

This case is typical of several of our adult SCD patients who have developed severe iron overload from sporadic blood transfusions.

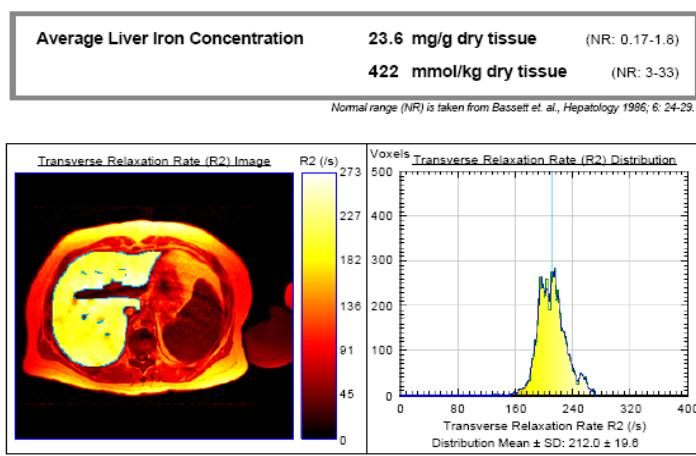
Myelodysplastic Syndrome Case Study

A 73-year old gentleman diagnosed with myelodysplasia in 2005, appears to have a stable form of myelodysplasia. He started transfusion in 2005, initially two-units every six weeks, but since 2006 three-units every four weeks.

The patient's ferritin at the time of referral was 2,943 μ g/l. He had a moderately low platelet count of 63 x 10⁹/l and was also mildly neutropenic. He has Type-II diabetes and is known to have angina. He had an increasing transfusion requirement and by December 2007 was requiring 3 units every 3 weeks to maintain his Hb at around 8g/dl.

The patient was started on desferrioxamine infusions when his ferritin level reached 3556 ug/l. He was unable to tolerate this and was started on Exjade® in Jan 2008. At this time he had a T2* cardiac and liver iron assessment which showed no myocardial iron loading but moderate liver iron loading at 7 mg/g/dw.

A FerriScan® was undertaken and this showed a liver iron of 23.6 mg/g/dw:



Liver Iron Concentration thresholds in Transfusional Iron Overload

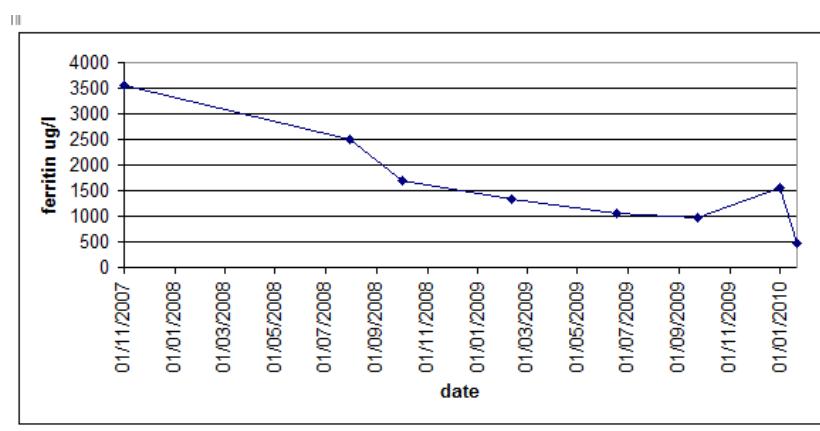
Extract from Olivieri et al, Blood 1997; 89, 739-61

LIC Range	Clinical Relevance
0.17-1.8 mg Fe/g dw	Normal range in non-disease patients in healthy population
3.2-7.0 mg Fe/g dw	Suggested optimal range of LIC for chelation therapy in transfusional iron loading
7.0-15.0 mg Fe/g dw	Increased risk of complications
> 15.0 mg Fe/g dw	Greatly increased risk of cardiac disease and early death in patients with transfusional iron overload

Intensive chelation therapy with Exjade was started at a 30mg/kg/day dose and careful monitoring of renal function was undertaken as initial creatinine was 80 μ g/l. The patient's creatinine rose to 123 ug/l by March 2008 and following a dose reduction to 25 mg/kg/day his renal function stabilised and returned to normal.

He continued on this dose of Exjade and by June 2009 his ferritin had fallen to 1057 ug/l. The patient had a dose reduction and is now on a maintenance dose of Exjade of 15 mg/kg/day. His transfusion requirement has reduced and he now receives 3 units of blood every 5 weeks.

Graph showing patient's serum ferritin levels over time



Serum ferritin and FerriScan in clinical management of iron overload in pediatric cancer survivors

Case Study 1: A 17 year old male with neuroblastoma (diagnosed at 2 years of age) subsequently had a bone marrow transplant (BMT) as part of his multi-modal treatment plan. Four years after his BMT, the serum ferritin (SF) measurement was 2991 microg/L. Given his high SF, he was subsequently phlebotomised for just over 2 years at which time his SF was reduced to 631 microg/L. A FerriScan measurement was also made at this time. At a level well below the commonly used SF screening threshold of 1000 microg/L, this survivor had a liver iron concentration (LIC) of 9 mg Fe/g, indicating he was still above the LIC threshold of 7 mg Fe/g where iron overload is still a concern. With the certainty and confidence FerriScan provided, phlebotomy treatment was therefore continued for another 2 years until his LIC returned to normal (2 mg Fe/g).

Average Liver Iron Concentration

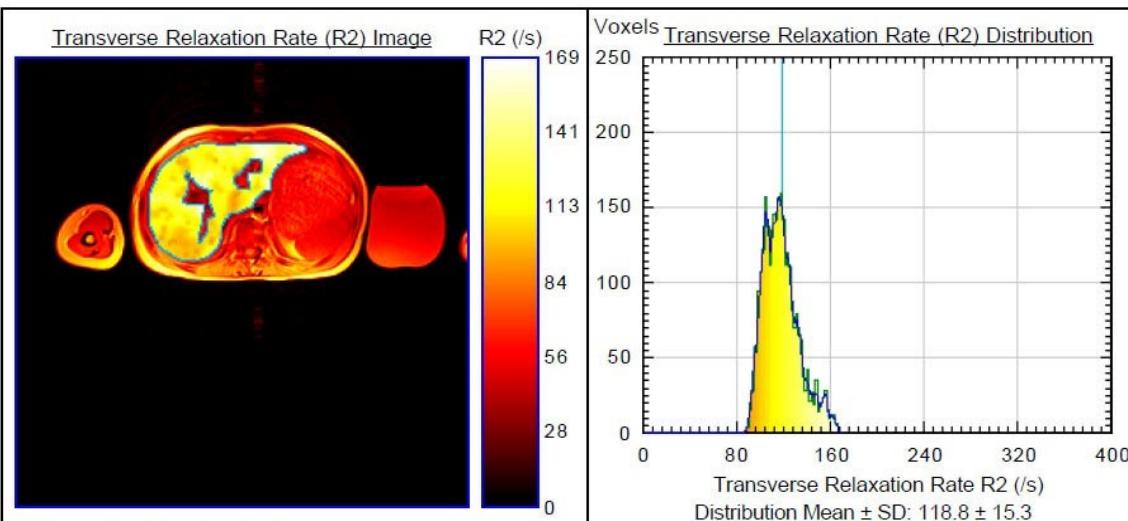
9.0 mg/g dry tissue

(NR: 0.17-1.8)

160 mmol/kg dry tissue

(NR: 3-33)

Normal range (NR) is taken from Bassett et. al., Hepatology 1986; 6: 24-29.

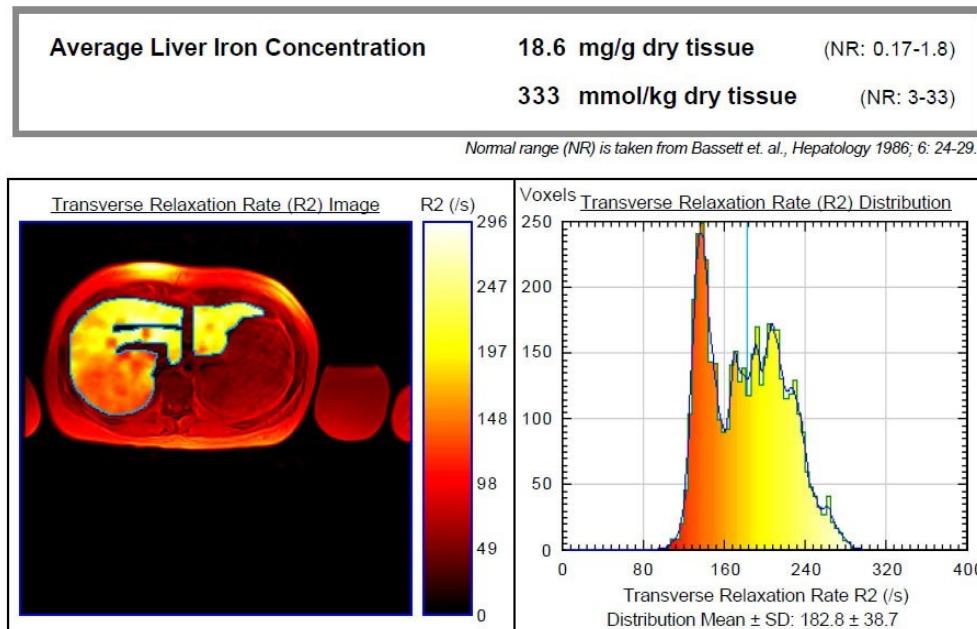


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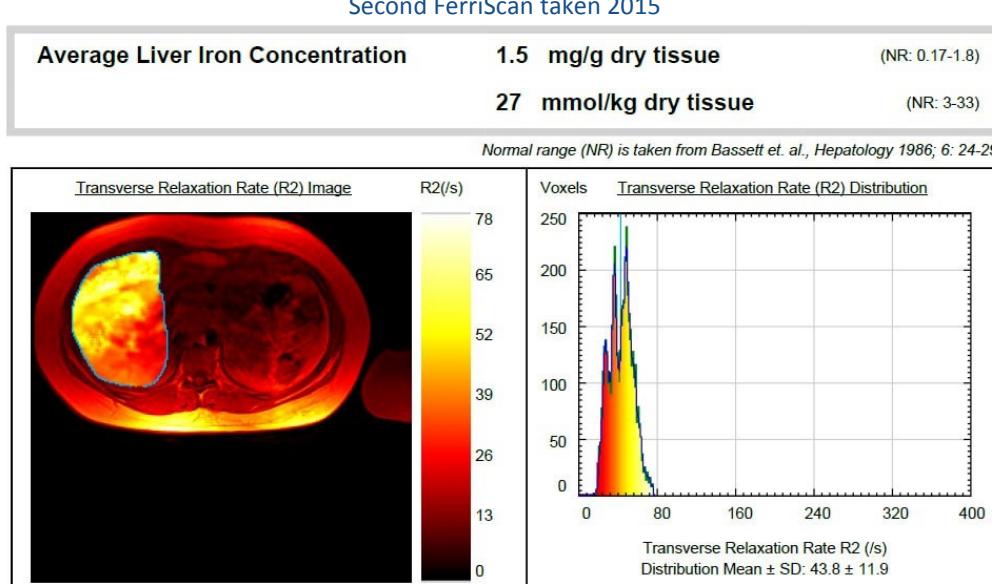
Cancer Survivor Case Study

Case Study 2: A 19 year old female with juvenile myelomonocytic leukemia (diagnosed at 5 years of age) received a bone marrow transplant (BMT) as part of her treatment. Her serum ferritin (SF) level seven years after treatment was 2189 microg/L and her liver iron concentration (LIC) was 18.6 mg Fe/g. Owing to her obvious iron overload she underwent phlebotomy treatment. After 30 months of regular treatment her SF had been reduced to 727 microg/L, but her LIC was still 6.6 mg Fe/g and so treatment was continued. Two years later her SF was 1187 microg/L, but had been consistently below 1000 microg/L in the previous two years. A FerriScan 2 months later returned an LIC of 1.5 mg Fe/g indicating her LIC had returned to normal levels despite her latest SF result. Without a FerriScan to confirm her LIC, phlebotomy treatment may have continued unnecessarily for this case.

First FerriScan taken 2010



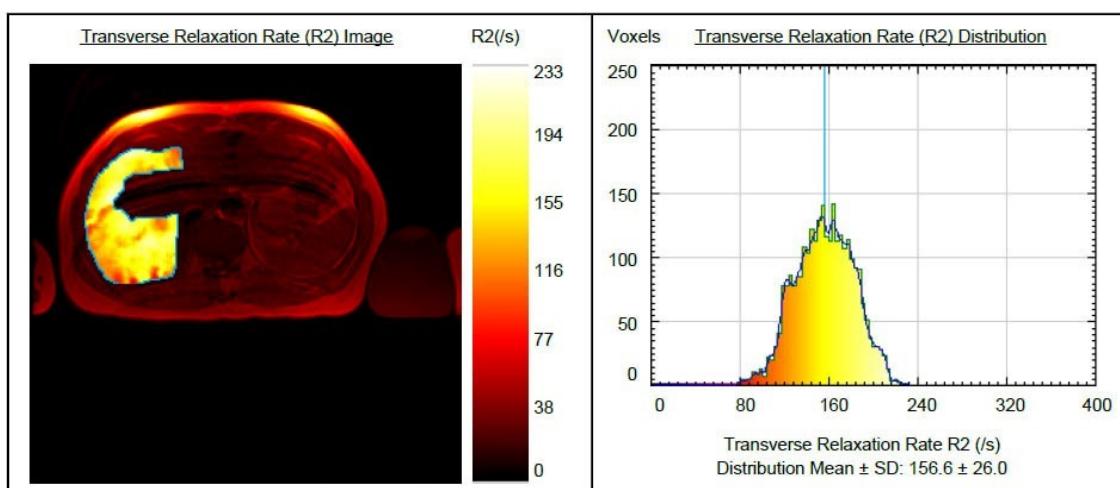
Second FerriScan taken 2015



Case Study 3: A 36 year old female survivor of acute myeloid leukemia (diagnosed at 14 years of age) did not receive a bone marrow transplant (BMT), but nearly 20 years after diagnosis iron overload was suspected and she was given a serum ferritin (SF) test which was 1011 microg/L. Around 6 months later she had a FerriScan and returned a liver iron concentration (LIC) of 13.7 mg Fe/g. Despite her borderline SF level, which in isolation may not have raised significant concern, the FerriScan result indicated that this case was close to approaching the very dangerous LIC level of 15 mg Fe/g and the care team was able to accordingly recommend phlebotomy for this patient.

Average Liver Iron Concentration	13.7 mg/g dry tissue	(NR: 0.17-1.8)
	245 mmol/kg dry tissue	(NR: 3-33)

Normal range (NR) is taken from Bassett et. al., Hepatology 1986; 6: 24-29



Note: The area of the liver image used for the FerriScan analysis excludes large vascular structures and other image artefacts.

Authorised by: Service Centre Manager

In summary, these case studies highlight that SF measurements taken in isolation can be misleading regarding the true iron status of these cancer survivors. Without a reliable estimate of LIC from FerriScan, cancer survivors may be at risk of unrecognised or misdiagnosed iron overload, leading to incomplete or even unnecessary treatment. When FerriScan is combined with simple phlebotomy treatment, the guess work is taken out of the clinical management of de-ironing cancer survivors.

Notes



MRI Measurement of Liver Iron Concentration

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info@resonancehealth.com