Pitfalls in the response evaluation after peptide receptor radionuclide therapy with $[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3]$ octreotate

Tessa Brabander¹, Wouter A van der Zwan¹, Jaap J M Teunissen¹, Boen L R Kam¹, Wouter W de Herder², Richard A Feelders², Eric P Krenning¹ and Dik J Kwekkeboom¹

¹Department of Radiology & Nuclear Medicine, Erasmus Medical Center, Rotterdam, The Netherlands
²Department of Internal Medicine, ENETS Center of Excellence, Erasmus Medical Center, Rotterdam, The Netherlands

Abstract

Peptide receptor radionuclide therapy (PRRT) with $[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3]$octreotate ($^{177}\text{Lu-DOTATATE}$) is a treatment with good results in patients with metastatic gastroenteropancreatic neuroendocrine tumours (GEPNETs). However, there are some pitfalls that should be taken into consideration when evaluating the treatment response after PRRT. 354 Dutch patients with GEPNETs who were treated with $^{177}\text{Lu-DOTATATE}$ between March 2000 and December 2011 were retrospectively selected. Liver function parameters and chromogranin A were measured before each therapy and in follow-up. Anatomical imaging was performed before therapy and in follow-up. An increase in aminotransferases by $\geq 20\%$ compared to baseline was observed in 83 of 351 patients (24%). In patients with an objective response (OR) and stable disease (SD) this increase was observed in 71/297 (24%) and in patients with progressive disease (PD) it was observed in 12/54 patients (22%). An increase in chromogranin A by $\geq 20\%$ compared to baseline was observed in 76 patients (29%). This was present in 34% of patients who eventually had PD and 27% of patients who had OR/SD. In 70% of patients this tumour marker returned to baseline levels after therapy. An increase in liver enzymes and chromogranin A is not uncommon after PRRT. In the vast majority of patients this will resolve in follow-up. Clinicians should be aware that these changes may occur due to radiation-induced inflammation or disease progression and that repeated measurements over time are necessary to differentiate between the two.

Introduction

Neuroendocrine tumours (NETs) are a rare type of cancer. The overall incidence rate for NETs has increased in the last few decades (Fraenkel et al. 2014). Unfortunately, the majority of patients have metastatic disease at the time of presentation (Korse et al. 2013). In the past decade a promising new treatment modality has been developed for inoperable or metastasized NETs. This peptide receptor radionuclide therapy (PRRT) uses radiolabeled somatostatin analogues. Since the majority of NETs express a high number of the somatostatin receptors on their cell membrane, this receptor can be used both for imaging and therapy of NETs with radiolabeled somatostatin analogues.
The most frequently used β-emitting radionuclides for PRRT are Yttrium-90 and Lutetium-177, linked to [DOTA\(^3\)Tyr\(^3\)]octreotide (\([\text{DOTA}\beta^3\text{Y}\text{DOTATOC}]\)) or [DOTA\(^3\)Tyr\(^3\)]octreotate (\([\text{DOTA}\beta^3\text{Lu}\text{DOTATATE}]\)), respectively. The objective response rate in patients with gastroenteropancreatic neuroendocrine tumours (GEPNETs) is 15–35% (Forrer et al. 2006, Kwekkeboom et al. 2008, Bushnell et al. 2010, Bodei et al. 2011, Imhof et al. 2011, Sabet et al. 2015). Recently, the results of the multicentre randomized phase III NETTER-1 trial in patients with advanced midgut NETs (Strosberg et al. 2017), comparing \(^{177}\text{Lu}\)-DOTATATE to high dose octreotide LAR therapy were presented. The progression free survival (PFS) in the group receiving octreotide LAR 60 mg was 8.4 months and was not reached for the group receiving \(^{177}\text{Lu}\)-DOTATATE plus 30 mg octreotide LAR (Hazard ratio 0.21; 95% CI 0.13–0.34). It may be expected that the number of patients treated with \(^{177}\text{Lu}\)-DOTATATE will increase in the coming years. Awareness of possible side-effects is important when treating patients with PRRT. The most frequently reported subacute side-effect is haematologic toxicity (Kwekkeboom et al. 2008, Sabet et al. 2013, Bodei et al. 2015). This toxicity is mostly mild and reversible. Late severe side-effects are myelodysplastic syndrome (MDS)/acute leukaemia (AL). Although 70–90% of patients with disseminated disease have metastases in the liver, reported hepatotoxicity is rare. Between treatment cycles patients undergo different blood tests to detect possible side-effects. These blood tests include haematology, renal and liver function parameters, and measurement of tumour markers. For response evaluation after therapy, imaging is done in addition to these blood tests. In 2013 van Vliet and coworkers demonstrated that there are no differences in the different response methods used in the follow-up of NET patients (van Vliet et al. 2013). When interpreting the blood tests and imaging during and directly after therapy some remarkable changes may occur, which are not in line with the final treatment response to therapy. Here, we present several pitfalls that might occur in the response evaluation during treatment and follow-up after PRRT with \(^{177}\text{Lu}\)-DOTATATE that the treating physicians should be aware of.

**Materials and methods**

**Patients**

354 Dutch patients with GEPNETs who were treated with \(^{177}\text{Lu}\)-DOTATATE between March 2000 and December 2011 were selected. Follow-up data was available until 2014. After 2011 most new patients returned to their referring specialist after therapy, so information about follow-up at our institute in these patients was limited. Inclusion criteria for therapy were: histologically proven metastatic or inoperable GEPNETS, tumour uptake at least equal to liver uptake on \(^{131}\text{In}\)-DTPA-octreotide scintigraphy, Karnofsky performance score (KPS) of at least 50, creatinine clearance ≥40 mL/min until 2007 or 50 mL/min from 2007, a platelet level of at least 75×10\(^3\)/L, a haemoglobin level of at least 6.0 mmol/L (9.7 g/dL), and a white blood cell count of at least 2.0×10\(^9\)/L. Only Dutch patients were selected, because of the limited loss in follow-up in this patient group. This study was part of the ongoing prospectively designed study in patients with NETs at our department and was approved by the local medical ethical committee. All patients gave their written informed consent to participate in the study.

**Treatment**

\([\text{DOTA}\beta^3\text{Tyr}\beta^3\text{octreotate}])\) was obtained from BioSynthema. \(^{177}\text{Lu}\)Cl\(_3\) was distributed by IDB-Nederland. \(^{177}\text{Lu}\)-DOTATATE was locally prepared as described previously (Kwekkeboom et al. 2001). 30 min before the infusion of \(^{177}\text{Lu}\)-DOTATATE was started, Granisetron 3 mg or Ondansetron 8 mg was injected intravenously. An infusion of amino acids (2.5% arginine and 2.5% lysine, 1 L) was started 30 min before the administration of the radiopharmaceutical as well and lasted for 4 h. The radiopharmaceutical was co-administered, using a second pump system. Cycle doses were 3.7 or 7.4 GBq (100 or 200 mCi), depending on short-term toxicity, injected over 30 min. The intended interval between treatments was 6–10 weeks. Normally, patients undergo 4 treatment cycles. Patients were treated up to an intended cumulative dose of 22.2–29.6 GBq (600–800 mCi).

**Anatomical imaging**

Computed tomography (CT) or magnetic resonance imaging (MRI) was performed at least 3 months prior to therapy. In follow-up, CT or MRI was performed 6 weeks, 3 months and 6 months after the last treatment and thereafter every 6 months. Tumour response was scored according to the Southwest Oncology Group (SWOG) solid tumour response criteria (Green & Weiss 1992), modified by adding a minor response (MR), pertaining to a decrease of 25–50% of the sum of measurable lesions. Patients were categorized according to confirmative tumour response 3 months after the last therapy.
Groups of patients with limited or extensive metastases in the liver were defined. Extensive liver disease was defined as diffuse metastases throughout the whole liver with hepatomegaly. Examples of patients with limited and extensive disease in the liver are presented in Fig. 1.

Blood examinations

Routine haematology, liver and kidney function parameters and chromogranin A were determined before each therapy, and at fixed follow-up visits. An increase of $\geq 20\%$ compared to baseline after the first therapy in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP) or chromogranin A (CgA) was considered clinically significant. ALP was measured as a total of all fractions (including bone and liver fractions).

Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

Statistics

Statistical analysis of the data was performed using Fisher’s exact test or chi-square test. A $P$-value $< 0.05$ was considered to be statistically significant.

Results

354 Dutch patients with GEPNETs were evaluated. Baseline characteristics are presented in Table 1. The most common primary tumour was located in the small intestine (46%), followed by the pancreas (31%). The vast majority of patients (86%) had metastases in the liver. Sixty-one patients (17%) had bone metastases. The mean age was 59 years (range 23–84 years).

A significant ($P < 0.05$) higher baseline level of the cholestatic liver enzymes GGT and ALP was observed in patients with extensive liver disease compared to patients with limited/no liver metastases. An increase of $\geq 20\%$ in GGT compared to baseline was observed in a total of 87 patients (25%) (Fig. 2 and Table 2). In patients with an objective response (OR) or stable disease (SD) this increase was seen in 72/293 patients (25%) and in patients with progressive disease (PD) it was seen in 15/54 patients (28%). Of the 87 patients with an increase of GGT, an increase of 1 CTCAE grade was seen in 33 patients (38%) and an increase of 2 grades was seen in 13 patients (15%).

An increase of $\geq 20\%$ in ALP compared to baseline was observed in 36/350 patients (10%). Of these 36 patients, 5 had bone metastases. The incidence of elevation was not significantly different from patients without bone metastases.

An increase in the aminotransferases (AST and/or ALT) by $\geq 20\%$ compared to baseline was observed in 83 of 351 patients (24%) (Table 2). In patients with OR/SD this increase was observed in 71/297 (24%) and in patients

Figure 1
Axial slices of CT’s of the upper abdomen in the arterial contrast phase. A and B are examples of patients with limited metastases in the liver. C and D are examples of patients with extensive metastases and enlargement of the liver.
with PD in 12/54 patients (22%). This increase was mild to moderate in all patients, with a maximum of 537 U/L. After an initial increase, the liver enzymes declined and eventually returned to baseline levels in the majority of patients during follow-up. In patients with OR/SD this increase was permanent in 9%, whereas in patients with PD a permanent increase was observed in 43% of patients. The albumin levels of these patients did not change significantly during therapy, bilirubin levels increased ≥20% compared to baseline in 20/83 of these patients (24%). Both patients with and without metastases in the liver showed a similar increase (Fig. 2). In patients without metastases an initial increase in aminotransferases was found in 17/43 patients (40%). This was permanent in 4/17 patients (24%). In 70% of patients with limited or no metastases in the liver, the mean enzyme level declined after the initial increase. In patients with extensive tumour load in the liver this decline was observed after the second therapy (Fig. 2). Of the 66 patients with an increase in AST, 35 (53%) had an increase of CTCAE of 1 grade, 2 patients (3%) had an increase of 2 grades and 3 patients (5%) had an increase of 3 grades. Of the 82 patients with an increase of ALT, 33 (40%) had an increase of 1 grade, 4 patients (5%) had an increase of 2 grades and 3 patients (4%) had an increase of 3 grades. No CTCAE grade 4 toxicity of AST/ALT was observed.

An increase of LDH was observed in 28 patients (8%). The baseline level of LDH was significantly higher in patients with extensive disease ($P<0.05$). The haemoglobin levels of these 28 patients did not change significantly after PRRT. Mean baseline level was 7.6 mmol/L and 12 weeks after PRRT the mean level was 7.3 mmol/L.

CgA was elevated in 265/354 patients. An increase of ≥20% after first therapy compared to baseline was observed...
in 76/265 patients (29%). This was present in 59/215 patients (27%) who had OR/SD and in 17/50 patients (34%) who eventually had PD. During the treatment cycles no differences of CgA between the response groups was found (Fig. 3). Twelve weeks after the last therapy the mean levels of CgA in patients with an OR/SD continued to decline, whereas the level of CgA in patients with PD showed a strong increase. In 19% of patients with OR/SD and 71% of patients with PD, the initial increase of CgA did not return to baseline levels.

In the group of patients with a complete response (CR) and partial response (PR) at 3 months follow-up, no increase in the tumour size was observed on the first CT in follow-up at 6 weeks after the last PRRT cycle. Of the 206 patients with SD (including MR), 18 patients (9%) had an increase of ≥10% in size at the first follow-up visit at 6 weeks after the last cycle of PRRT. The median increase in size was 18% (range 10–71%). In 16/18 patients this increase was below 50% and in 2/18 patients there was an increase of ≥50%. An example is given in Fig. 4. During follow-up the sum diameter of lesions eventually declined in 50% of patients at 6 months follow-up with a median decrease of 27%. PD as outcome at 3 months follow-up and based solely on an increase in size of measurable lesions of more than 50% occurred in 3 patients out of 54 patients with PD. In the remaining 51/54 patients (94%) new lesions or clear deterioration in clinical condition determined permanent PD.

**Discussion**

In this study, we identified several pitfalls that should be taken in consideration when evaluating the response to treatment in patients treated with $^{177}$Lu-DOTATATE. These temporary changes during and directly after therapy have not been described previously. There are many reports about haematologic and renal toxicity (Gupta et al. 2012, Sabet et al. 2013, Bergsma et al. 2015, Svensson et al. 2015), while reports about hepatotoxicity after PRRT are rare (Bushnell et al. 2003, Riff et al. 2015). From experience with external beam radiation therapy it is known that radiation-induced liver disease or radiation hepatitis can be a serious problem, which can result in liver failure and even death. Radiation-induced liver disease typically presents 4–8 weeks after therapy (Lawrance et al. 1995), especially as increased ALP, but aminotransferases can be elevated as well. The whole liver can recover from a radiation dose of 30 Gy without permanent damage. During treatment with $^{177}$Lu-DOTATATE the radiation dose to the liver remains well below 30 Gy (Kwekkeboom et al. 2001), explaining the very low radiation-induced liver disease after PRRT. Liver failure after PRRT with $^{90}$Y

---

Table 2  
Number of patients with an increase of biochemical markers ≥20% after first therapy compared to baseline value.

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th></th>
<th>SD</th>
<th></th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>n</em></td>
<td></td>
<td>Increase (%*)</td>
<td>Permanent (%**)</td>
<td></td>
<td>Increase (%*)</td>
</tr>
<tr>
<td>ALP</td>
<td>94</td>
<td>6 (6)</td>
<td>1 (17)</td>
<td>202</td>
<td>22 (11)</td>
</tr>
<tr>
<td>GGT</td>
<td>92</td>
<td>16 (17)</td>
<td>2 (13)</td>
<td>205</td>
<td>56 (27)</td>
</tr>
<tr>
<td>AST</td>
<td>91</td>
<td>16 (18)</td>
<td>1 (6)</td>
<td>205</td>
<td>39 (19)</td>
</tr>
<tr>
<td>ALT</td>
<td>88</td>
<td>24 (27)</td>
<td>2 (8)</td>
<td>205</td>
<td>46 (22)</td>
</tr>
<tr>
<td>LDH</td>
<td>88</td>
<td>10 (11)</td>
<td>1 (10)</td>
<td>200</td>
<td>13 (7)</td>
</tr>
<tr>
<td>CgA</td>
<td>68</td>
<td>14 (21)</td>
<td>1 (7)</td>
<td>147</td>
<td>45 (31)</td>
</tr>
</tbody>
</table>

*Increase: % of n (OR/SD/PD); **permanent: % of increased n.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CgA, chromogranin A; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase.

Figure 3: Evolution of chromogranin A after an initial increase of ≥20% after first therapy. Presented as mean levels of CgA. CgA, chromogranin A; CR, complete remission; MR, minor response; PD, progressive disease; PR, partial remission; PRRT, peptide receptor radionuclide therapy; SD, stable disease.
and/or \textsuperscript{177}Lu labelled somatostatin analogues is reported rarely, and is most commonly due to progressive disease. In patients treated with \textsuperscript{90}Y microsphere radioembolization, a radiation-induced liver disease grade 2–3 is reported in 0–4\% of patients (Kennedy & Salem 2010). A report from Ezziddin and coworkers found mostly minor (no grade 4) liver toxicity in 23 patients after treatment with \textsuperscript{90}Y microspheres as a salvage therapy after failed PRRT with \textsuperscript{177}Lu-DOTATATE (Ezziddin et al. 2012). We found a mild to moderate (CTCAE grade 1–3) increase in aminotransferases in 24\% of patients, which was reversible in most patients. Since the level of albumin did not change, the hepatocyte function seems not to be affected. Both in patients with OR/SD and PD, there was an increase in aminotransferases that was not different between these response groups. Also an increase of serum ALP was observed after the first therapy. An elevated ALP can be indicative of liver toxicity or obstruction, but can also be due to a high bone turnover, caused by bone metastases. However, no differences in ALP between patients with and without bone metastases were found. Also an increase of LDH can have different causes. The haemoglobin level of these patients did not change during therapy, so haemolysis is probably not the cause of this increase. A recent report of Jimenez-Fonseca and coworkers demonstrated that an elevated LDH is associated with a worse prognosis compared to patients with a normal LDH (Jimenez-Fonseca et al. 2016). The present results show that patients with extensive metastases in the liver had a higher baseline level of LDH. In 2008 we demonstrated that patients with extensive liver involvement have a shorter survival than patients with limited or no metastases in the liver (Kwekkeboom et al. 2008). These findings are concordant with the report by Jimenez-Fonseca and coworkers.

The published reports about hepatotoxicity after PRRT are not consistent. A recent report from Riff and coworkers showed an episode of hepatotoxicity in 59\% of patients treated with \textsuperscript{90}Y-DOTATOC and/or in combination with \textsuperscript{177}Lu-DOTATOC (Riff et al. 2015). Besides radiopharmaceuticals, patient features also differ from our study and may explain the difference between the reported hepatotoxicity. A number of patients in the report from Riff and coworkers were treated with radioembolization or other liver-directed therapies before PRRT, whereas in our study no patient underwent previous radioembolization. Furthermore, the hepatotoxicity in our study was temporary and reversible in 91\% of patients with OR/SD and 57\% of patients with PD.

Bushnell and coworkers (Bushnell et al. 2003) found an increase of one WHO grade in at least one liver enzyme in 9 of 15 patients with liver metastases after the first treatment of \textsuperscript{90}Y-DOTATOC. In only 4 patients this increase was still present 4–6 weeks after the third and last therapy. In patients without liver metastases one of six patients had an increase after three therapies. No significant relation was found between the extent of hepatic metastases and the increase in liver enzymes. The results from this small study are more consistent with our data than the above-mentioned study from Riff and coworkers (Riff et al. 2015). None of the patients from
the study of Bushnell and coworkers had prior liver-directed therapy.

The pattern of an initial increase followed by normalization in follow-up has also been described for haematologic toxicity after PRRT. Sierra and coworkers reported a grade 2–3 B-cell lymphocyte toxicity after each cycle in 14 of 16 patients (Sierra et al. 2009). All types of lymphocyte toxicity eventually resolved after 90 days. Kulkarni and coworkers described mildly elevated serum creatinine in 5/22 patients directly after PRRT (Kulkarni et al. 2013). However, serious renal toxicity is very rare after treatment with $^{177}$Lu-DOTATATE and occurs in less than 1% of patients (Bodei et al. 2008, Sabet et al. 2014), provided that appropriate renal protection by lysine/arginine infusion is applied.

CgA is a protein that is present in the secretory granules of most neuroendocrine cells (Deftos 1991). In patients with NETs it can be used as a tumour marker, since it is excreted together with the peptide hormones in the neurosecretory granules (O’Connor & Deftos 1986, Nobels et al. 1998). Although CgA is a nonspecific marker for NETs, well-differentiated NETs often have an elevated level of CgA, which is positively correlated with a tumour burden. If elevated, it is a useful marker to evaluate biochemical response to therapy or progression. After the first cycle with $^{177}$Lu-DOTATATE an increase of ≥20% in CgA was observed in 29% of our patients. No differences were found between the different response groups. Therefore, this increase did not indicate progression in most patients and may be explained by a release of CgA due to radiation-induced cell damage or lysis. The decline of CgA after the initial peak supports this hypothesis. Also in patients with PD the CgA declined after an initial peak. In follow-up, not until 12 weeks after the last cycle of PRRT, a difference in CgA between PD and non-PD patients occurs. To avoid undertreatment, patients should, therefore, not be considered as progressive based on an increase of CgA during or shortly after PRRT. In a small number of patients the increase in liver enzyme and CgA levels did not return to baseline levels during follow-up. This was seen more often in patients with PD compared to those with OR/SD and this increase is, therefore, more likely to be tumour progression related.

This phenomenon is not unique: in patients with well-differentiated thyroid carcinoma treated with radioactive iodine therapy, a transient increase in the biochemical marker thyroglobulin (Tg) directly after radioactive iodine ablation has been described. Similar to PRRT in NETs, it was suggested that this increase is due to tissue destruction/inflammation. During follow-up, the Tg levels fall below baseline levels after 6 months (Stivic et al. 2015). This transient increase of Tg is even considered as a prognostic indicator of the success of the radioactive iodine treatments (Bernier et al. 2005).

A change in CgA may also occur after the start and during the use of somatostatin analogues. A total of 16/76 patients with an increase of CgA used PPIs during PRRT and 33/76 of patients used somatostatin analogues. Three patients started PPIs during therapy, this may have an influence on the evolution of CgA during therapy. Although due to the small number of patients, the potential effect on the increase of CgA is, therefore, limited.

The proliferation marker Ki-67 can be used for the grading of NETs (Rindi et al. 2006, 2007). In 2007 we started to use Ki-67 routinely for all NETs. This study included patients treated from 2000 and therefore the Ki-67 is not available for all patients. It is, therefore, not possible to correlate the grading to the incidence of increase of CgA and liver enzymes.

An increase of the diameter of lesions of 10% or more on imaging was seen in 9% of patients with SD at 6 weeks post PRRT and was reversible at 6 months follow-up in 50% of patients. This transient increase was probably caused by inflammation causing localized oedematous tissue at the site of the metastases and not based on progression. This radiogenic oedema has been described previously for PRRT of brain tumours and external beam radiation (Kneifel et al. 2006, Barani & Larson 2015). In studies with cytokines, cancer vaccines and monoclonal antibodies an increase in tumour burden has been demonstrated in patients with CR, PR or SD as treatment outcome. This phenomenon was described as pseudo-progression and resulted in a new response method, the immune-related response criteria (irRC) (Wolchok et al. 2009). This increase in the tumour size after immunotherapy is probably related to infusion of lymphocytes and macrophages in the tumour and new lesions are not always considered as PD. In our study, a temporary increase in tumour size was only observed in NET patients with SD as treatment outcome. Furthermore, it is notable that in 51/54 of the PRRT patients who eventually had PD as treatment outcome, it was based on the finding of new lesions on imaging or clinical deterioration. In 3 of 54 patients who had PD as treatment outcome, it was based solely on an increase of the diameter of the lesions according to SWOG criteria. The irRC are, therefore, not applicable for NET patients. Also, due to the low frequency of radiation-induced inflammation after PRRT, it seems that a new response method for NET patients is
not required. However, clinicians should be aware that an increase in size directly after PRRT is more frequently due to radiation-induced inflammation than to permanent disease progression.

Conclusion

In this study we found that a temporary increase in liver function parameters and CgA level is not uncommon after treatment with PRRT, and it is not related to the final response to therapy at 3 months post PRRT. Since CgA may be released during cell damage, this increase does not pertain to progression in most patients. No differences were found between patients with an OR/SD and PD. Therefore, both liver function parameters and CgA should be interpreted with caution during therapy. Lastly, a temporary increase of ≥10% in the size of metastases is not uncommon after the intended cycles of PRRT. Our observations reported in this study indicate that initial permanent progression based on imaging is virtually always reflected by the finding of new lesions and rarely by an increase in tumour size alone. Clinicians should be aware that initial diameter increases are more frequently due to temporary radiation-induced inflammation than due to permanent disease progression, and that repeated imaging over time is necessary to differentiate between the two.


Received in final form 16 March 2017
Accepted 20 March 2017
Accepted Preprint published online 20 March 2017