[\textsuperscript{18}F]-Fluorodeoxyglucose Positron Emission Tomography and Computed Tomography in Response Evaluation of Oncolytic Adenovirus Treatments of Patients with Advanced Cancer

Anniina Koski, Helena Ahtinen, Heidi Liljenback, Anne Roivainen, Anu Koskela, Minna Oksanen, Kaarina Partanen, Leena Laasonen, Kalevi Kairemo, Timo Joensuu, and Akseli Hemminki

Abstract

Computed tomography (CT) is the most commonly used radiological response evaluation method in contemporary oncology. However, it may not be optimally suitable for assessment of oncolytic virus treatments because of paradoxical inflammatory tumor swellings, which result from virus treatments, particularly when viruses are armed with immunostimulatory molecules. Here we investigated the prognostic utility of CT and [\textsuperscript{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) in oncolytic virus treatments. We also investigated possible appearance of false-positive FDG signals in FDG-PET imaging of humans and hamsters treated with oncolytic adenoviruses. First, immunocompetent Syrian hamsters were treated with intratumoral adenovirus injections, tumor growth was followed up, and [\textsuperscript{18}F]-FDG-uptake was quantitated with small animal PET/CT. Second, we describe a retrospective patient series, essentially 17 individual case reports, of advanced cancer patients treated with oncolytic adenoviruses in the context of an Advanced Therapy Access Program (ATAP) who underwent radiological response evaluation with both contrast-enhanced CT and FDG-PET. Third, we collected a retrospective case series of radiological response and survival data of 182 patients treated with oncolytic adenoviruses in ATAP to evaluate the prognostic reliability of CT and FDG-PET. Overall, responses in CT and FDG-PET correlated well with each other and were equally reliable as prognostic markers for long survival after oncolytic adenovirus treatment. Interestingly, we observed that new FDG-avid lymph nodes appearing in FDG-PET after virus treatments may represent inflammatory responses and therefore should not be interpreted as treatment failure in the absence of other signs or verification of disease progression. We also observed indications that FDG-PET might be more sensitive in detection of responses than tumor size.

Introduction

ONCOLYTIC VIRUSES ARE PROMISING NOVEL CANCER TREATMENTS making progress in clinical trials. One product has already reached market approval in China, and there are numerous phase 1–3 clinical trials ongoing also in the Western countries (Garber, 2006; Eager and Nemunaitis, 2011). Currently, contrast-enhanced computed tomography (CT) is the leading method for radiological response evaluation, and anatomical criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) are frequently used for the characterization of responses in trials (Eisenhauer et al., 2009). These evaluation standards have been suitable in traditional treatment approaches such as chemotherapy, where tumor shrinkage (“response”) has been measured as a sign of treatment benefit (Wolchok et al., 2009). With immunotherapy, including oncolytic viruses, responses are elicited in a more complex way, involving the activation of the immune system, and therefore also radiographic patterns of response differ from those of traditional chemotherapeutics. In the case of immunologically active treatments, initial increase in tumor diameter may indicate mounting of an inflammatory
response to the treatment instead of progression (Wolchok et al., 2009; Hoos et al., 2010). This has been exemplified in trials where patients receiving oncolytic viruses have first had paradoxical increases in tumor size, followed by tumor shrinkage (Sze et al., 2003, 2011; Reid et al., 2005). Tumors may also remain stable for extended periods before eventual shrinkage of the tumor or a clinically insignificant metabolically inactive residual tumor may remain after treatment. Also, immunotherapy can impact patient survival even in the absence of effects on tumor size (Kantoff et al., 2010). All these situations might be falsely interpreted as treatment failure using standard anatomical response evaluation (Wolchok et al., 2009; Hoos et al., 2010). If this leads to premature attenuation of therapy, it could be against the interest of the patient.

Positron emission tomography (PET) using [18F]-fluorodeoxyglucose (FDG) measures tissue metabolism based on quantification of glucose uptake. Increased consumption of glucose is a characteristic of most cancers and therefore uptake of FDG is a sign of tumor cell viability, whereas reductions in tumor FDG uptake can represent antitumor efficacy (Young et al., 1999). Therefore, FDG-PET is a useful tool for diagnosis, staging, restaging, and treatment monitoring of many tumor types (Hoh, 2007; Kumar et al., 2009; Baksh et al., 2012; Radhakrishnan et al., 2012). In fact, the biological predictive value of PET appears greater than anatomic imaging studies in certain cancer types, especially early during therapy (Wahl et al., 2009). On the other hand, glucose uptake of inflammatory cells is high and inflammatory processes can thus lead to problems in interpretation of FDG-PET in oncology (Shrieve et al., 1999). For example, there have been observations of false-positive FDG-PET findings in lymphoma patients after influenza vaccinations (Focosi et al., 2008). This implies that also oncolytic virus treatments could lead to falsely positive signals in FDG-PET, for example, in local lymph nodes subsequent to induction of immunological responses.

In this study, we aim to investigate the usefulness of FDG-PET in oncolytic adenovirus treatments and to compare FDG-PET and CT as prognostic surrogates in advanced cancer patients treated with oncolytic adenoviruses. The hypothesis is that FDG-PET imaging could have advantages over CT by being more sensitive in detecting responses and predicting survival benefits in patients. We also aimed to determine if adenovirus treatments such as may lead to false-positive signals in FDG-PET imaging.

Materials and Methods

Cell lines and adenoviruses

HapT1 hamster pancreatic carcinoma-derived cell line was kindly provided by Dr. Ruben Hernandez-Alcoceba (University of Navarra, Madrid, Spain). A549 human lung cancer cell line was purchased from American Type Culture Collection (ATCC, Manassas, VA). Cells were stored and cultured in recommended conditions.

Ad5wt is a wild-type Ad5 (Ad300wt strain) purchased from ATCC. Ad5-D24-GMCSF and Ad5/3-D24-GMCSF have been described before and are both oncolytic adenoviruses armed with human granulocyte-macrophage colony stimulating factor (GMCSF) (Cerullo et al., 2010; Koski et al., 2010). Viruses were propagated on A549 cells and adenoviral preps were prepared according to standard protocols.

Animals

Syrian hamsters (Mesocricetus auratus) were obtained at 11 weeks of age, and quarantined for 2 weeks. All animal protocols were reviewed and approved by the Provincial Government of Southern Finland and the Experimental Animal Committee of the University of Helsinki. Animals were euthanized if tumors grew over set limits (≥20 mm in diameter) or the general condition of animals deteriorated. Anesthesia for cell injections was performed with fentanyl citrate 0.315 mg/kg, flunisone 10 mg/kg, and midazolam 5 mg/kg diluted in sterile water. Anesthesia for other procedures was performed with isoflurane inhalation.

Syrian hamster model

Hamsters (n=4–6/group) were injected subcutaneously with 1×107 HapT1 cells at four different sites. Virus injections were given on days 1, 4, 8, and 15 intratumorally in a volume of 50 μl per tumor, starting when tumors were ~8 mm in diameter. Each treatment comprised 1.125×109 VP/tumor for Ad5wt and Ad5-D24-GMCSF and 1.125×1010 VP/tumor for Ad5/3-D24-GMCSF, diluted in sterile saline (0.9% NaCl). Mock treatment comprised saline only. For Ad5/3-D24-GMCSF group, one tumor per hamster was mock injected with saline. Tumor size was measured by external caliper and volumes were calculated (4/3·π·[0.5·width]2·[0.5·length]). The slope for tumor volume growth over time was calculated with linear assumption.

Two hamsters per group were imaged with FDG-PET/CT on days 1 (baseline before injections), 2, 3, 8, 10, and 16 with a dedicated small animal PET/CT scanner (Inveon Multimodality; Siemens Medical Solutions, Knoxville, TN). After 4 hr fasting, the hamsters were anesthetized with isoflurane and injected intraperitoneally with FDG (15±8 MBq). After the CT for attenuation correction, PET was performed at 90 min postinjection. Blood glucose levels were measured with a glucometer (Accu-Check Aviva; Roche Diagnostics, Mannheim, Germany). Data acquired for 20 min in a list mode were iteratively reconstructed with the ordered-subsets expectation maximization 3D algorithm.

Quantitative PET analysis was performed by defining volumes of interest on the tumor (Inveon Research Workplace 3.0; Siemens Medical Solutions). FDG uptake was reported as maximum standardized uptake value (SUV) normalized for average blood glucose level. Maximum SUV (SUVmax) is the single most active voxel in the lesion. The slope for SUVmax change over time was calculated with linear assumption. The ratio of tumor volume slope to tumor SUVmax slope was calculated for each tumor.

After the last PET/CT on day 16, hamsters were immediately euthanized. Tumors, tissue samples, urine, and blood were collected, weighed, and measured for radioactivity with a gamma counter. The radioactivity was reported as blood glucose-corrected SUV.

Patients

Oncolytic adenovirus treatments were given in the context of an Advanced Therapy Access Program (ATAP), which is under regulation of Finnish Medical Agency as determined by EU/1394/2007. Written informed consent was required from patients, and treatments were administered according
to the Declaration of Helsinki and Good Clinical Practice. ATAP is in compliance with EU and Finnish regulations and has been evaluated by The Gene Technology Board and Medicolegal Department of the Finnish Ministry of Social Affairs and Health. Data for this study were collected and analyzed retrospectively from the ATAP treatments, with approval from Helsinki University Central Hospital ethics committee (Onro 62/13/03/02/2013). All ATAP treatments administered between 2007 and 2012, for which CT or PET imaging data were available, were included.

The general nonbinding criteria for patient treatment in ATAP include solid tumors refractory to conventional therapies and progressive disease (PD), WHO performance score ≤ 3, and no major organ function deficiencies. The general criteria for exclusion were organ transplant, HIV or other major immunosuppression, brain metastasis, bilirubin, ALT or AST elevated > 3 over upper limit of normal, thrombocytopenia ≤ 75 x 10^9/liter, or other severe disease or organ malfunction. All patients were heavily pretreated but had not received oncolytic virus treatments previously. Details of baseline characteristics are in Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/hum). Many of the patients described in this patient series have also been published previously (Cerullo et al., 2010, 2011; Koski et al., 2010, 2012; Nokisalmi et al., 2010, 2011; Pesonen et al., 2010, 2012a,b; Rajeki et al., 2011; Raki et al., 2011; Ranki et al., 2011; Bramante et al., 2012; Hemminki et al., 2012; Liikanen et al., 2012). Here we summarize the data on radiological response evaluations.

### Treatment protocols and follow-up

Patients (n=182) received the virus treatments performed mainly by ultrasound (rarely by CT-guided) intratumoral injection. Treatments (n=421) were given as single treatments or in a series of three treatment cycles approximately 3 weeks apart. In the case of intraperitoneal or intrapleural disease, “intratumoral” injection could be performed also intracavitarily. One-fifth of the dose was typically administered intravenously, and if there were no injectable lesions, the whole dose was given intravenously. Summaries of treatments are in Supplementary Table S1. After treatment, patients were monitored for 24 hr in the hospital and for at least 4 weeks as outpatients.

### Anatomical response evaluation

Tumor sizes were assessed by contrast-enhanced CT before and after treatment for 121 patients. For baseline scans, only scans within 28 days before the first viral treatment were considered evaluable. For five patients, anatomical evaluation was performed by magnetic resonance imaging (MRI). Follow-up scans were performed after a median of 3 cycles of virus treatments (range 1–3 cycles) at a median of 63 days after the first virus treatment (range 20–99). Maximum tumor diameters were determined according to RECIST 1.0 and RECIST 1.1 (Therasse et al., 2000; Eisenhauer et al., 2009), including injected and noninjected lesions. As a modification to the criteria, tumor decreases of 10–29%, not fulfilling

### Table 1. Response Assessment Classifications

<table>
<thead>
<tr>
<th>Anatomical evaluation</th>
<th>Metabolic PET evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response</strong></td>
<td>Disappearance of all tumor lesions, no new metastatic lesions.</td>
</tr>
<tr>
<td><strong>Partial response</strong></td>
<td>&gt;30% reduction in the sum of tumor diameters, no new metastatic lesions.</td>
</tr>
<tr>
<td><strong>Minor response</strong></td>
<td>10–29% reduction in the sum of tumor diameters, no new metastatic lesions.</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>0–9% reduction or up to ≤20% increase in sum of tumor diameters, no new metastatic lesions.</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>≥20% increase in sum of tumor diameters or appearance of new metastatic lesions.</td>
</tr>
<tr>
<td><strong>Disease control</strong></td>
<td>Stable disease, minor response, partial response, or complete response.</td>
</tr>
</tbody>
</table>

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B. Based on RECIST v1.1.

B. Based on PERCIST. As modification, new lymph node signals were not considered automatically as disease progression, as the role of inflammation caused by virus treatment cannot be ruled out.

CT, computed tomography; FDG, [18F]-fluorodeoxyglucose; PET, positron emission tomography; SUV, standardized uptake value; RECIST, Response Evaluation Criteria In Solid Tumors; PERCIST, PET Response Criteria In Solid Tumors.
partial response, were scored as minor responses. Response classifications are summarized in Table 1.

**Metabolic response evaluation**

FDG-PET, together with low-resolution anatomical CT, was performed before the first viral treatment and after median of 3 cycles of virus treatments (range 1–3 cycles), median 71 days after the first virus treatment (range 52–126). Approximately 5 MBq/kg of FDG was injected after a 4–6 hr fasting. Blood glucose levels were measured and image acquisitions typically started 50–70 min afterward with acquisition time 3–4 min/bed position. The follow-up scans were performed with similar acquisition parameters as the pretreatment scans. The 18F-FDG doses in the follow-up studies did not generally differ more than ±20% from the pretreatment doses. The time from injection to start of acquisition was optimally the same or within 15 min in the pre- and posttreatment scans.

The evaluation of treatment response followed the philosophy of PET Response Criteria In Solid Tumors (PERCIST) 1.0 (Wahl et al., 2009) with some modifications (Table 1). SUV_{max} and SUV_{peak} values were recorded for quantification of FDG metabolic activity. SUV_{peak} was measured using a 1.15 cm³ sphere containing the single most active voxel in the lesion. The most active lesions in study one were compared with the most active lesions in study two. As suggested by Wahl et al. (2009), measurements were recorded from up to five hottest foci (no more than two foci/organ) and summed SUV values were compared between the two studies (not necessarily the same lesions if other lesions had become more active). Tumor decreases of 10–29%, not fulfilling partial metabolic response, were scored as minor metabolic responses. In the modified FDG-PET evaluation new lymph node signals were not considered automatically as disease progression.

Optimally pre- and posttreatment FDG-PET scans were performed with the same equipment. However, as these patients were treated in a treatment program, not a trial, this was not always possible, which is a common situation also in practical oncology. Therefore, in a few cases SUV values between baseline and follow-up PET scans were not optimally comparable, because of technical differences in acquisitions. In these cases isotope radiologists analyzed the images visually. In PERCIST 1.0, appearance of new metastatic lesions is graded as progressive metabolic disease (PMD). Therefore, even if exact SUV changes are not quantifiable, but visually there was clear appearance of new metastatic FDG-avid lesions, these cases (n=5) were graded as PMD.

**Dual-imaging patient series**

Both contrast-enhanced CT and FDG-PET were obtained from 17 patients before and after 3 cycles of oncolytic adenovirus treatments administered approximately every 3 weeks. Follow-up imaging was conducted at a median of 70 days (range 63–85 days) after the first virus treatment. CT and PET responses were assessed as described above. Tumor markers were also evaluated after treatments if they had been elevated previously. The percentage change at a median of 22 days (range 6–64 days) after the latest virus treatment cycle was reported, using the same percentages as for CT evaluations. Alterations in symptoms were assessed with a three-tier classification (improvement, stable, or worse) based on patient interviews and clinical examination at the follow-up visit ~1 month after the latest virus treatment.

**Statistics**

Statistics were done with IBM SPSS Statistics 20 and MedCalc software. Hamster tumor growth was compared with mixed model for fixed effects. Slopes and FDG uptake to tissues were analyzed by Student’s t-tests. Patient survival data were processed with Kaplan–Meier analysis, Log rank test, and Log rank test for trend. Comparison of the number of CT and FDG-PET responses and absolute decreases in SUV_{max} and tumor size were conducted with Fisher’s exact test. Cohen’s χ² or Pearson coefficients were calculated for correlations. Comparison of baseline characteristics and treatments in the CT and FDG-PET extension patient series were performed by Fisher’s exact test, χ²-test, and Student’s t-test. For tumor types, only those with at least altogether three cases and for concomitant therapies the three most common were included in the statistical comparison.

**Results**

**Syrian hamster model**

The treatment doses corresponded weight-to-weight to human dose of $3 \times 10^{11}$ VP for a 66 kg person. Tenfold higher dose was used with Ad5/3-D24-GMCSF, because of lower permissivity of Syrian hamsters for chimeric Ad5/3 than Ad5 (Cerullo et al., 2010; Koski et al., 2010; Bramante et al., 2012). There was no difference in tumor growth between mock- and Ad5/3-D24-GMCSF-injected tumors. Although this experiment was not designed for efficacy, we observed a trend for slower tumor growth in Ad5-D24-GMCSF group ($p=0.14$ vs. mock) (Supplementary Fig. S1A).

We observed a peak in tumor FDG uptake after the first injection in FDG-PET imaging of most animals, including mock-treated hamsters (Supplementary Fig. S1B; Fig. 1). This may indicate an inflammatory response to the injection procedure. For mock-treated animals, change in SUV_{max} seemed to correlate with tumor size (Fig. 1A), whereas for hamsters treated with adenoviruses, FDG uptake plateaued after the initial peak. The plateau was even clearer with the oncolytic viruses armed with GMCSF (Fig. 1B and C). These differences were reflected in the slopes of the tumor size and FDG-uptake growth curves, with on average negative SUV_{max} slopes for virus-treated groups ($p<0.05$) and negative ratios of tumor volume slopes to FDG-uptake slopes in groups treated with GMCSF-encoding viruses ($p<0.05$) (Fig. 1E and F). This is compatible with FDG-PET being more sensitive in detecting early signs of response as compared with tumor volume.

After the last PET-CT, FDG uptake in tissues and tumors was measured *ex vivo* (Fig. 1G; Supplementary Fig. S1C). Lymph nodes were of particular interest, as inflammatory reactions caused by the virus treatment might cause increased metabolism in them. We observed that tumor FDG uptake was lower in Ad5wt and Ad5/3-D24-GMCSF groups compared with mock ($p<0.05$). Interestingly, FDG uptake in lymph nodes of Ad5/3-D24-GMCSF-treated animals was higher than that in mock-treated hamsters ($p<0.05$). There were also similar trends in the Ad5-D24-GMCSF group (Fig. 1G and H).
Treatment responses evaluated by contrast-enhanced CT and FDG-PET

Here we describe a set of 17 individual cases of patients who were imaged with both contrast-enhanced CT and FDG-PET before and after 3 cycles of oncolytic adenovirus treatments (Table 2). These results were obtained in the context of a retrospective case series study. (See Table 2 for details of virus treatments and individual responses.) In this retrospective patient series, four patients had disease control (DC) in RECIST v1.1 evaluation of the CT scans. Out of these, 3 patients had stable disease and 1 patient had continuation of radiological complete response, and 13 patients had progressive disease (PD). Median survival of patients with DC was 361 days and with PD 229 days ($p = 0.068$) (Fig. 2A and B; Table 3).

PET responses were evaluated according to summed SUV$_{\text{max}}$ values, but also the corresponding summed SUV$_{\text{peak}}$ values were recorded (Table 2). As expected, SUV$_{\text{max}}$ and SUV$_{\text{peak}}$ values correlated very well with each other, with a Pearson coefficient of 0.97 ($p < 0.0001$). Five patients were determined to have metabolic disease control (MDC), out of which two patients had stable metabolic disease, one patient had partial metabolic response, one patient had minor metabolic response, and one patient had continuation of a complete metabolic response. Twelve patients had progressive metabolic disease (PMD). Median survival of patients with MDC was 361 days and with PMD 229 days ($p = 0.367$) (Fig. 2C and D; Table 3).

In the FDG-PET scans, new FDG-avid lymph nodes were detected in two patients without other signs of disease progression. Conventionally, these lymph node signals should be interpreted as disease progression (Wahl et al., 2009). However, they may likely be indicative of an inflammatory response related to treatment, as implied also by our hamster experiment (Fig. 1). Therefore, PET response evaluation was performed also by not considering these as signs of progression. In this modified evaluation, both of these patients had stable metabolic disease. According to the modified PET criteria, median survival of the 7 patients with MDC was 362 days and the 10 patients with PMD was 203 days ($p = 0.079$).

The modified PET criteria identified 7/17 patients as possibly benefiting from oncolytic virus therapy, versus 4/17 patients identified with CT, and thus PET identified 75% more patients. Although this difference was not statistically significant in this small series, it may be relevant as it is compatible with FDG-PET being a more sensitive way to detect treatment effects. The median survival of these 7 versus 4 patients was 362 and 361 days, respectively, suggesting that there was no loss of specificity. Likewise, in 65%
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<th>Viruses$^b$</th>
<th>Dose (VP)</th>
<th>Route</th>
<th>Time$^c$ (days)</th>
<th>RECIST v1.1 (%)</th>
<th>FDG-PET (%SUV$<em>{max}$/%SUV$</em>{peak}$)</th>
<th>Tumor marker responses</th>
<th>Clinical symptoms</th>
<th>Survival$^d$ (days)</th>
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<td>PMD</td>
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<td>PD</td>
<td>PMD</td>
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(continued)
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<tr>
<th>Patient ID</th>
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<th>Tumor marker responses</th>
<th>Clinical symptoms</th>
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<td></td>
<td></td>
<td>Ad5/3-hTERT-CD40L</td>
<td>3×10&lt;sup&gt;11&lt;/sup&gt;</td>
<td>100% i.t.</td>
<td></td>
<td></td>
<td>(+63%; new) (−19%/−20%)</td>
<td>(CEA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S241</td>
<td>Malign fibrotic histiocytoma</td>
<td>2</td>
<td>ICOVIR-7</td>
<td>4×10&lt;sup&gt;12&lt;/sup&gt;</td>
<td>100% i.v., 50% i.t.</td>
<td>63</td>
<td>PD</td>
<td>PMD (Stable)</td>
<td>(CEA)</td>
<td></td>
<td>125</td>
</tr>
<tr>
<td>I244</td>
<td>Choroideal melanoma</td>
<td>1</td>
<td>Ad5/3-hTERT-CD40L</td>
<td>1×10&lt;sup&gt;11&lt;/sup&gt;</td>
<td>100% i.t.</td>
<td>70</td>
<td>SD</td>
<td>SMD (Stable)</td>
<td></td>
<td></td>
<td>361</td>
</tr>
<tr>
<td>C246</td>
<td>Rectum carcinoma</td>
<td>2</td>
<td>Ad5/3-hTERT-CD40L</td>
<td>3×10&lt;sup&gt;11&lt;/sup&gt;</td>
<td>100% i.t.</td>
<td>70</td>
<td>PD</td>
<td>MMR (PD)</td>
<td>Improvement</td>
<td>229</td>
<td></td>
</tr>
<tr>
<td>R247</td>
<td>Breast carcinoma</td>
<td>2</td>
<td>Ad5/3-d24-GMCSF</td>
<td>3×10&lt;sup&gt;11&lt;/sup&gt;</td>
<td>100% i.t.</td>
<td>84</td>
<td>MR</td>
<td>PMR (SD)</td>
<td>Improvement</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>R248</td>
<td>Breast carcinoma</td>
<td>1</td>
<td>Ad5/3-d24-GMCSF</td>
<td>3×10&lt;sup&gt;11&lt;/sup&gt;</td>
<td>100% i.t.</td>
<td>77</td>
<td>PD</td>
<td>SDM (PD)</td>
<td>Improvement</td>
<td>393</td>
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Baseline and treatment characteristics and radiological and clinical responses for patients (n=17) for whom both contrast-enhanced CT, evaluated according to RECIST v1.1, and FDG-PET were performed simultaneously before and after three cycles of treatments with oncolytic adenoviruses. Percentage change in tumor diameters and appearance of new lesions indicated for CT and percentage change in summed SUV, as well as appearance of new FDG-avid lesions for FDG-PET in parentheses.

<table>
<thead>
<tr>
<th>Time&lt;sup&gt;c&lt;/sup&gt;</th>
<th>RECIST v1.1 (%)</th>
<th>FDG-PET (%SUV&lt;sub&gt;max&lt;/sub&gt;/%SUV&lt;sub&gt;peak&lt;/sub&gt;)</th>
<th>Tumor marker responses</th>
<th>Clinical symptoms</th>
<th>Survival&lt;sup&gt;d&lt;/sup&gt;</th>
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<sup>a</sup>Baseline status according to WHO performance criteria.

<sup>b</sup>See references for viruses (Cerullo et al., 2010; Koski et al., 2010; Nokisalmi et al., 2010; Pesonen et al., 2010, 2012a,b; Ranki et al., 2011; Hemminki et al., 2012).

<sup>c</sup>Time in days from first viral treatment to radiological response evaluation.

<sup>d</sup>Overall survival after first virus treatment.

<sup>e</sup>Complete radiological response continues from previous treatment.

<sup>f</sup>Patient alive at latest follow-up, August 2013.

FDG-avid lymph nodes detected, but not confirmed to be metastatic.

CEA, carcinoembryonic antigen; CMR, complete metabolic response; CR, complete response; i.t., intratumorally; i.v., intravenously; MMR, minor metabolic response; NSE, neuron-specific enolase; PD, progressive disease; PMD, progressive metabolic disease; SD, stable disease; SMD, stable metabolic disease.
FIG. 2. FDG-PET and contrast-enhanced CT. Radiological responses in patients imaged with both contrast-enhanced CT and FDG PET, expressed as percentage change in tumor size and summed SUV\textsubscript{max}. (A) Patients arranged in a waterfall plot according to percentage change in tumor size as determined by RECIST. (B) Patients were grouped according to CT responses to having either disease control (DC; solid line) or progressive disease (PD; dashed line), and their overall survival was plotted by a Kaplan–Meier. (C) Patients arranged in a waterfall plot according to percentage change in tumor summed SUV\textsubscript{max}. (D) Patients were grouped according to PET responses to having either metabolic disease control (MDC; solid line) or progressive metabolic disease (PMD; dashed line), and overall survival was plotted by a Kaplan–Meier. In (D) new FDG-avid lymph nodes were considered a sign of metabolic progression and in (E) new FDG-avid lymph nodes were not automatically considered as a sign of metabolic progression. (F) Patients were grouped by having either disease control according to both CT and FDG-PET (n = 4, black line), mixed responses between CT and FDG-PET (n = 4, gray line), or disease progression according to both CT and FDG-PET (n = 10, dashed line), and overall survival was plotted by a Kaplan–Meier. n = 17 patients. Vertical ticks in Kaplan–Meier plots indicate patients who were still alive in August 2013 and therefore censored (n = 2). DC, disease control; MDC, metabolic disease control; PD, progressive disease; PMD progressive metabolic disease.
## Table 3: Summary of Responses and Survival of Patients

<table>
<thead>
<tr>
<th>Response evaluation</th>
<th>Median survival according to response</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>PD or MDC (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DC or MDC (%)</td>
</tr>
</tbody>
</table>

### Dual-imaging patient series

- **RECIST 1.1**
  - 17 patients
  - PD: 6 (35%), MDC: 11 (65%)
  - Median survival: 293 days (95% CI: 188–426 days)
  - Hazard ratio: 1.67 (0.57–4.52)

- **FDG-PET**
  - 21 patients
  - PD: 7 (33%), MDC: 14 (67%)
  - Median survival: 261 days (95% CI: 167–355 days)
  - Hazard ratio: 1.67 (0.45–6.32)

- **Modified FDG-PET**
  - 21 patients
  - PD: 3 (14%), MDC: 18 (86%)
  - Median survival: 293 days (95% CI: 188–426 days)
  - Hazard ratio: 1.67 (0.45–6.32)

### Tumor markers

- Evaluable (elevated at baseline) for 13 patients.
- Median survival: 203 days (95% CI: 138–268 days)
- Hazard ratio: 0.75 (0.17–3.09)

### Clinical symptoms

- Evaluable for 17 patients.
- Median survival: 361 days (95% CI: 174–548 days)
- Hazard ratio: 0.95 (0.33–2.69)

### Extended Anatomical imaging

- 121 patients
- Median survival: 376 days (95% CI: 204–548 days)
- Hazard ratio: 2.62 (2.00–4.42)

### Metabolic/FDG-PET

- 79 patients
- Median survival: 336 days (95% CI: 272–400 days)
- Hazard ratio: 2.27 (1.49–3.97)

**Correlations of anatomical and metabolic responses**

For the 17 individual cases where both FDG-PET and CT response data were available, percentage change in tumor size and summed SUV<sub>max</sub> correlated only weakly with each other (Pearson coefficient of 0.28, p = 0.269). Notably, 7/17 patients had an absolute decrease in SUV<sub>max</sub> and only 1/17 had an absolute decrease in tumor size (p = 0.032) (Fig. 2A and C). This is compatible with a higher sensitivity of PET for detecting possible treatment benefits.

In this retrospective patient series overall, responses evaluated by contrast-enhanced CT and FDG-PET were concordant in 14/17 patients (82%) (Table 2). The value for Cohen’s κ for the correlation was 0.55 (p = 0.022), indicating moderate correlation (Supplementary Table S2). Using the modified PET criteria, where new FDG-avid lymph nodes were allowed, response correlation was better, with Cohen’s κ 0.61 (p = 0.006). New metastatic lesions were detected in CT scans of 10 patients and new FDG-avid lesions in pattern typical of tumor in FDG-PET scans of 10 patients; these correlated moderately well with Cohen’s κ of 0.51 (p = 0.035). Notably, there were no new lesions in the contrast-enhanced CT images of the two patients who had new FDG-avid lymph nodes in absence of other signs of progression in FDG-PET, suggesting that these were false-positives because of induction of an immune response.

The median survival for patients with DC in both radiological evaluation methods (n = 4) was 361 days, median survival for patients with mixed responses (n = 3, all of these were MDC with PET and PD with CT) was 362 days, and for patients with progression by both methods (n = 11) was 203 days (Fig. 2F). The differences in survival between between patients with DC in both imaging modalities and patients with MDC in PET but PD in CT were not significant, although there was a statistically significant linear trend (p = 0.049) between the groups. The three “mixed” cases are particularly interesting as they would have been classified as “progressors” with CT but, nevertheless, had a median survival equivalent to patients with DC with both methods, suggesting that using CT alone would miss many patients possibly benefiting from therapy.

In this small series of 17 individual patients, responses in serum tumor marker levels or clinical symptoms did not correlate significantly with radiological responses, each other, or overall survival (Table 2; Supplementary Table S2).

### Extended patient series

We collected all patients for whom radiological response evaluation was performed after oncolytic adenovirus treatments in ATAP between 2007 and 2012 (Supplementary Table S1). In this retrospective case series study, there were 121 patients with anatomical radiological response evaluation and 79 patients with metabolic FDG-PET response evaluation (Table 3). Baseline characteristics of patients in these two series were well balanced with regard to sex (p = 0.65), age (p = 0.58), and WHO performance score at baseline (p = 0.21) and major tumor types (p = 0.514).
With regard to treatments, there were differences in the dose, route of administration, type of treatment, treatment viruses, and use of concomitant therapies between these patient series (all \( p < 0.05 \)), reflecting the nonconcurrent nature of these patient series (CT was used initially and FDG-PET later) (Supplementary Table S1). Therefore, direct comparison of, for example, response rates between these groups should not be made.

Anatomical response evaluations in extended patient series

One hundred twenty-one patients were imaged with contrast-enhanced CT, or in a few cases MRI. Responses were evaluated according to RECIST when appropriate. In cases where tumors were not evaluable by RECIST (\( n = 27 \)), for example, because of their shape or location (e.g., carcinomatosis, skin or bone metastases, pleural lesions), response assessment was based on overall radiological interpretation. Thirty patients (25%) were determined to have stable diseases, 8 patients (7%) had minor responses, 2 patients (2%) had partial responses, and 4 patients (3%) had complete responses, including two cases of continuation of previous radiological complete response. Therefore, 44 patients (36%) were classified as having DC after therapy. Forty-two patients had new metastatic lesions in the follow-up scans, and altogether 77 patients (64%) were determined to have PD. Median survival of patients with DC was 376 days and with PD 158 days (\( p < 0.0001 \)) (Table 3; Fig. 3A). If only patients for whom formal RECIST evaluation was available (\( n = 96 \)) were included, 37 patients (39%) had DC and 57 patients (61%) had PD, and median survival with DC was 376 days and with PD 189 days (\( p < 0.0001 \)) (Table 3; Fig. 3B; Supplementary Fig. S2A).

Immune-related response criteria (irRC) have been suggested for evaluation of immunotherapeutic cancer treatments (Wolchok et al., 2009). The irRC are based on conventional WHO response criteria with bidimensional tumor measurements. In this patient series, CT response evaluation was based on the more recent RECIST criteria, with unidimensional tumor measurements. Therefore, the irRC were not applicable on this patient series as such. However, in the spirit of the irRC, we subdivided patients with PD into having either “clear PD” or “mild PD,” the latter including...
patients with new metastatic lesions but less than 20% increases in RECIST sum and patients with no new lesions but small increases (20–30%) in RECIST sum. Median survival with clear PD was 157 days, with mild PD 195 days and with DC 376 days ($p<0.0001$ for linear trend between groups). Survival with DC was longer than with either mild PD or clear PD ($p<0.0001$), but there was no significant difference between mild PD and clear PD ($p=0.575$, Supplementary Fig. S2). Therefore, mild PD did not seem to be very effective in identifying patients possibly benefitting from therapy.

**Metabolic response evaluations in the extended patient series**

Seventy-nine patients were imaged with FDG-PET, and responses were evaluated according to summed $SUV_{\text{max}}$ with the modified PET criteria; that is, new FDG-avid local lymph node signals were not considered as progression in the absence of other signs of progression (Fig. 3C and D). Fourteen patients (18%) had stable metabolic disease, 8 patients (10%) had minor metabolic response, 4 patients (5%) had partial metabolic response, and 6 patients (8%) had complete metabolic response, including 4 cases of continuation of previous radiological complete metabolic response (see examples in Fig. 3E–G). Therefore, total of 32 patients (41%) had MDC. Forty-seven patients (59%) had PMD. Out of these, new FDG-avid lesions typical of tumor were recorded in follow-up scans of 46 patients, indicating that almost all cases of metabolic progression were associated with new tumor lesions. Median survival of patients with MDC was 336 days and with PMD 187 days ($p<0.0005$) (Table 3; Fig. 3).

A higher proportion of patients had an absolute decrease in $SUV_{\text{max}}$ compared with tumor size (35% vs. 16%, $p=0.01$) (Fig. 3). This is compatible with the hypothesized higher sensitivity of PET. However, since the patient series were nonconcurrent, with some variations in the treatments schedules (Supplementary Table S1), a formal sensitivity analysis cannot be performed reliably in this larger population. Nevertheless, the median survivals of all patients imaged with CT or PET were comparable (219 vs. 229 days), and WHO performance score distribution was similar ($p=0.21$), suggesting that the populations were similar.

**Discussion**

In the Syrian hamster model, tumor $SUV_{\text{max}}$ corresponded well to tumor growth in the mock-treated hamsters, as expected. Both Ad5-D24-GMCSF and Ad5/3-D24-GMCSF have previously demonstrated potent antitumor efficacy in this model (Cerullo et al., 2010, 2011; Koski et al., 2010). However, this is an aggressively growing tumor model and for this experiment, tumors were grown to larger size than usual before commencement of virus injections, to ensure measurability in PET imaging (Cerullo et al., 2010, 2011; Koski et al., 2010). Therefore, it is not surprising that significant tumor volume reductions were not observed during the short timeline of this experiment. In addition, as the experiment was not designed for efficacy, the dose and schedule may not have been optimal for these hamsters with larger than usual tumor sizes and human equivalent dosing. Therefore, optimization might have been useful for optimal response if efficacy would have been the main endpoint of the hamster experiment. However, since the goal was to assess imaging methods, the current setup was chosen. Nevertheless, in groups treated with the oncolytic viruses, there was a trend for plateau in FDG uptake while tumor volume was still increasing, which is compatible with FDG-PET recognizing antitumor effects before signs of tumor volume decrease. Importantly, when tumor FDG activity was measured ex vivo, the tumor FDG uptake in virus-treated groups was on average twofold lower than in mock treated, indicating antitumor efficacy. These findings highlight that FDG-PET may be useful in response assessment and more sensitive than CT in early detection of possible treatment benefits.

We described a series of 17 individual cancer patients who had been imaged with both contrast-enhanced CT and FDG-PET before and after oncolytic adenovirus treatments. For these patients, CT and FDG-PET responses correlated moderately well with each other. There was a clear trend for longer survival for patients with DC in both CT and FDG-PET evaluation, but these differences were not statistically significant in this small series. Of note is that if new FDG-avid lymph nodes were considered automatically a sign of progression, the trend between survival of patients with MDC versus PMD was not as clear. This suggests that these lymph node signals may not actually represent progression but could instead indicate induction of the immune response, as predicted by virus design: GMCSF expression is expected to boost antitumoral immune responses (Dranoff, 2003; Arellano and Lonial, 2008; Prestwich et al., 2009). The data from the hamster experiment also supports this notion, as hamsters treated with the immunostimulatory oncolytic adenovirus Ad5/3-D24-GMCSF had highly active lymph nodes detected simultaneously with reduction of tumor metabolism. Therefore, we propose, while larger studies on the matter are surely needed, that in oncolytic virus treatments new signals in local lymph nodes should not be interpreted as progression in FDG-PET in the absence of other signs of progression, unless unequivocally proven so by other methods. The extended patient series was thus analyzed without considering new FDG-avid lymph nodes as metabolic progression in FDG-PET.

In the extended analysis, we included all patients who had received oncolytic adenovirus treatments in the ATAP and for whom a radiological response evaluation was available. Patients with DC based on anatomical imaging had significantly longer survival compared with patients with PD. Similarly, for patients evaluated with FDG-PET, MDC was prognostic for significantly longer survival. We also investigated if patients with mild PD in CT evaluation would have better prognosis than with clear PD, in the spirit of the irRC suggested for immunotherapeutics (Wolchok et al., 2009), but there was no difference between these subsets of patients with regard to overall survival.

With regard to sensitivity of the methods, both the hamster and human data suggested that PET may be more sensitive in detecting antitumor effects. In hamster imaging, tumor $SUV_{\text{max}}$ plateaued in groups receiving potent oncolytic virus treatments before signs of tumor size reduction. In the patient series, there was a trend for more DC responses detected in FDG-PET imaging than CT, and there were significantly more absolute $SUV_{\text{max}}$ reductions than tumor size reductions. This has relevance for execution of clinical trials
with response rate or DC as an endpoint. Moreover, identification of patients possibly benefiting from therapy would be useful in routine clinical use to avoid misinterpretation of progression, so that patients are not needlessly switched to further therapies. Finally, FDG-PET has the additional advantage of identifying viable tumor areas, which can be useful for intratumoral injections of oncolytic viruses, which replicate only in living tumor cells.

To our knowledge, direct comparisons between FDG-PET and contrast-enhanced CT have not been attempted previously in the context of oncolytic adenoviruses. However, Sze et al. treated 22 colorectal carcinoma patients with liver metastases using intra-arterial hepatic administration of a vector based on herpes simplex virus 1 in a phase I/II trial (Sze et al., 2011). The investigators observed that late FDG-PET and CT responses correlated with each other and clinical outcomes, but concluded that addition of FDG-PET to contrast-enhanced CT did not provide useful diagnostic or prognostic data (Sze et al., 2011). In our small retrospective 17-patient series, the concordance between CT and FDG-PET responses was good and also FDG-PET responses alone had as reliable prognostic value as CT responses. In contrast to the experience of Sze et al. with herpes (Sze et al., 2011), we believe that FDG-PET may be more sensitive and therefore useful in response evaluation of oncolytic adenoviruses. A possible reason for this contrasting data could involve the viral platform. Sze et al. used an unarmed herpes virus (Sze et al., 2011), while in ATAP, adenoviruses, in most cases armed with immunostimulatory transgenes, were used. However, both observations arose from relatively small patient series in nonrandomized settings and thus larger patient populations may be required to demonstrate possible advantages of each technology.

In summary, in the retrospective patient series study presented here, anatomical response evaluation based on RECIST and metabolic response evaluation based on FDG-PET were both reliable in recognizing patients who had longer survival after treatments. Interestingly, data from both the Syrian hamster model and cancer patients suggested that FDG-avid lymph nodes after treatment may be a sign of inflammatory response to the virus and therefore should not be automatically interpreted as progression of disease. As elegantly demonstrated for CT response evaluation of the immunotherapeutic ipilimumab (Wolchok et al., 2009), it is also important to observe the development of responses in a longer follow-up. In this patient series, posttreatment evaluations were typically available only at a single time point. Therefore, additional evaluations at longer time intervals would also be useful. For these reasons, the ongoing early phase trials with Ad5/3-D24-GMCSF (a.k.a. CGTG-102) incorporate radiological response evaluation with a combination of contrast-enhanced CT, analyzed according to both RECIST1.1 and irRC, and FDG-PET at multiple time points. Further work is needed in adopting irRC (Wolchok et al., 2009; Hoos et al., 2010) in the context of oncolytic virus treatments, and similar separate guidelines for assessing immune-related and/or viral therapies by means of FDG-PET may also be needed. Nevertheless, while waiting for confirmation in randomized trials, the data reported here suggest that both CT and FDG-PET can be used prognostic surrogates for oncolytic adenoviruses, and that FDG-PET may be more sensitive.

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Author Disclosure Statement

A.H. is a shareholder of and consultant to Oncos Therapeutics Ltd. A.H. is an employee and shareholder of TILT Biotherapeutics Ltd.

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