



What are the consequences of routine reductions for DPD deficient patients in radical chemoradiation for anal squamous cell carcinoma?

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Complete List of Authors:	Jones, Hayley; Oxford University Hospitals NHS Foundation Trust, Department of Oncology Gilbert, Duncan; Brighton and Sussex University Hospitals NHS Trust, Sussex Cancer Centre Gilbert, Alex; St James' Hospital, Leeds Cancer Centre Jacobs, Clare; Oxford University Hospitals NHS Foundation Trust, Department of Oncology Muirhead, Rebecca; Oxford University Hospitals NHS Foundation Trust, Department of Oncology
Keywords:	DPD testing, anal squamous cell carcinoma, dose reductions
Abstract:	Letter to Editor The routine implementation of dose reductions in patients with dihydropyrimidine dehydrogenase (DPD) testing is increasing. In the recently published paper by Glynn-Jones et al, the impact of reduced dose chemotherapy in chemoradiotherapy (CRT) for patients with anal squamous cell carcinoma of the anus (ASCC) was quantified. They reported a statistically significant reduction in all cancer outcomes, in patients receiving a reduced chemotherapy dose. We highlight the relevance of this data in decisions regarding dose reductions in this highly curable tumour and consider alternative strategies.

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Consequences of routine reductions for DPD deficient patients in radical chemoradiation for squamous cell anal cancer.

Hayley Jones¹, Duncan Gilbert², Alex Gilbert³, Clare Jacobs¹, Rebecca Muirhead¹

1 Department of Oncology, Oxford University Hospital NHS Foundation Trust, Oxford, UK

2 Sussex Cancer Centre, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK

3 Leeds Cancer Centre, St James' University Hospitals, Leeds, UK

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Corresponding author

Dr Rebecca Muirhead,
Consultant in Clinical Oncology,
Level 2 Cancer Offices
Department of Oncology,
Cancer and Haematology centre,
Churchill hospital,
Oxford, UK.
OX3 7LE
Email: rebecca.muirhead@oncology.ox.ac.uk
Telephone: +44 1865 235 209

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Dear Sir,

Glynn-Jones et al [1] investigated the impact of reduced dose chemotherapy in chemoradiotherapy (CRT) for patients with anal squamous cell carcinoma of the anus (ASCC). They reported a statistically significant reduction in all cancer outcomes in patients receiving a reduced dose. We wish to highlight this data in the context of dihydropyrimidine dehydrogenase (DPD) testing.

DPD is a critical enzyme required in the metabolism of fluoropyrimidines. 9% of the population have polymorphisms in the DPYD gene resulting in low levels of DPD activity and 0.5% lack the enzyme completely. This deficiency increases the risk of severe toxicity from fluoropyrimidines. In March 2020, the European Medicines Agency recommended that all patients due to receive fluoropyrimidines be

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3 tested. They recommend that fluropyrimidines are not used for patients with complete deficiency,
4 and a dose reduction advised for those with partial deficiency [2].
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8 However, in deciding whether dose reductions are appropriate, it is important to consider the relative
9 loss of efficacy (with poorer cancer outcomes) versus the increased risk of significant toxicities due to
10 undiagnosed DPD deficiency who received full dose treatment. Glynne-Jones et al. compared patients
11 who received chemotherapy as per protocol versus those that had a delay, dose reduction or both to
12 their week 5 chemotherapy. It must be acknowledged for those patients randomised to Cisplatin / 5-
13 Fluorouracil in week 5, the breakdown of cisplatin / 5-fluorouracil is not provided in the paper. They
14 reported a statistically significant reduction in 3-year overall survival (OS) from 86% to 77% and
15 progression free survival (PFS) from 75% to 66% with reduced dose. This reduction was most marked
16 in locally advanced tumours where the absolute OS and PFS fell by 22% and 21% respectively. The risk
17 of life-threatening toxicity or incapacity/disability from DPD deficiency, prior to DPD testing, was 1.6%
18 [3]. Many of these deaths were from toxicities not identified by many DPD tests such as ischaemic
19 events or peripheral neuropathy. The is death rate is similar to that from a recent series of 385 anal
20 cancer patients treated with CRT for ASCC (1%) [4]. Of these deaths only 0.2% were due to a known
21 adverse effect of fluoropyridimine.
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35 One strategy to manage DPD deficiency in ASCC without routine dose reductions is the substitution of
36 capecitabine rather than 5-fluorouracil [5]. The standard capecitabine dose in CRT for ASCC is already
37 60% of that used as monotherapy in metastatic colorectal cancer. Daily oral administration allows
38 early reduction or discontinuation of the drug if toxicity arises (assuming regular monitoring of
39 haematological and non-haematological toxicity), or conversely commencing at a reduced dose and
40 increasing as tolerated. Since the routine implementation of DPD testing at Oxford University Hospital,
41 we identified two patients with heterogeneous DPD deficiency. Following consent, both patients were
42 treated with full dose capecitabine with increased monitoring; and both haematological and non-
43 haematological toxicity did not exceed Grade 2 throughout treatment.
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51 Given the important findings highlighted by Glynne-Jones et al we urge ongoing efforts to understand
52 the implications of DPD testing, treatment decisions and outcomes in ASCC.
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- [1] Glynne-Jones R, Meadows HM, Lopes A et al. Impact of compliance to chemoradiation on long-term outcomes in squamous cell carcinoma of the anus. Results of a post-hoc analysis from the randomized phase III ACT II trial, *Ann Oncol* 2020. DOI:<https://doi.org/10.1016/j.annonc.2020.06.012>
- [2] European Society for Medical Oncology 2020. EMA provides new testing and treatment recommendations for fluorouracil, capecitabine and tegafur. ESMO, viewed 14/07/2020, <<https://www.esmo.org/oncology-news/ema-provides-new-testing-and-treatment-recommendations-for-fluorouracil-capecitabine-and-tegafur>>
- [3] Barin-Le Guellec, C. Lafay-Chebassier, C. Ingrand, I. et al. Toxicities associated with chemotherapy regimens containing a fluoropyrimidine: A real-life evaluation in France. *European Journal of Cancer* 2020;124:37-46
- [4] Shakir, R. Adams, R. Cooper, R. et al. Patterns and predictors of relapse following radical chemoradiation therapy delivered using intensity modulated radiation therapy with a simultaneous integrated boost in anal squamous cell carcinoma. *Int Radiat Onc Biol Phys* 2020;106:329-339
- [5] Jones, CM. Adams, R. Downing, A. et al. Toxicity, Tolerability, and Compliance of Concurrent Capecitabine or 5-Fluorouracil in Radical Management of Anal Cancer With Single-dose Mitomycin-C and Intensity Modulated Radiation Therapy: Evaluation of a National Cohort. *Int J Radiat Oncol Biol Phys* 2018;101:1202-1211