Dose-response to different radiochemotherapy regimens in locally advanced pancreatic cancer

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Abstract. Conformal radiation therapy (RT) delivered concomitantly with chemotherapy including 5-fluorouracil (5-FU) or Gemcitabine (GEM) is a common treatment for patients with unresectable locally advanced pancreatic tumors. In this study, the Poisson model describing tumor response to these two treatment options was derived. Clinical data was retrieved from reports published from 1990 to 2015. Dosimetric and clinical data from 1196 patients treated with RT with concurrent 5-FU or GEM were gathered. RT doses ranging from 3.6-64.8 Gy, delivered in fractions of 1.2-8 Gy, were converted to a 2 Gy fractionation scheme using the Biological Effective Dose concept. The parameters of the Poisson-Linear-Quadratic-Time model were derived using genetic algorithm optimization to minimize the least-square fitting error. The goodness of the fit was assessed using the Pearson χ^2-test. For RT+5-FU, D_{50} was 56.5 Gy, γ was 3, α/β was 4.4, T_{pot} was 36 days and Tk was 23 days. For RT+GEM, D_{50} was 48.3 Gy, γ was 3, α/β was 6.4, T_{pot} was 36 days and Tk was 23 days. As expected, RT+GEM showed higher efficacy than RT+5-FU. A RT dose-response effect was obtained showing that treatment strategies allowing a dose-escalation in pancreas tumors should be investigated.

Keywords: Pancreas Tumors, Dose-Response Models, Radiation Therapy, Chemotherapy.

1 Introduction

Pancreatic tumors are amongst the most challenging cancer types. Patients are generally diagnosed with the disease in advanced stages for which surgery is no longer viable. Different chemotherapy regimens delivered alone or in combination with RT, have largely been used without achieving long-term overall success. Survival rates are thus

generally poor and consensus about the best treatment option for each patient has not been established [1].

In concomitant radiochemotherapy, the most common chemotherapy agents are 5-fluorouracil (5-FU) and gemcitabine (GEM). These have frequently been used as single agents but have also been combined with different regimens [2-34]. Better overall survival and progression-free survival was generally obtained with radiochemotherapy based on the GEM agent compared to the 5-FU [35,36]. Interestingly in a network meta-analysis that compared different GEM regimens, the combination of RT with GEM has shown to be the most effective GEM based treatment compared to the combination of GEM with other chemotherapy drugs [37]. With conformal RT, dose-prescription were mostly confined to values between 50.4-59.4 Gy. A dose escalation appears to be beneficial in terms of local control, progression-free survival and overall survival [27,33,35,38], but limited by the tolerance of surrounding organs at risk. An accurate model describing tumor response to delivered treatments is thus very useful as it may help investigating new treatment approaches for pancreatic cancer.

The aim of this study was to derive the dose-response parameters for the Poisson-Linear-Quadratic-Time model for locally advanced pancreatic tumors for patients that received conformal RT concomitant with 5-FU or GEM using the clinical data reported in the literature.

2 Material and methods

Clinical information was retrieved from scientific papers reporting treatment outcome of patients with locally advanced pancreatic cancer (cases with distant metastasis were excluded). Primary treatment was 3D conformal RT concurrent with 5-FU or GEM and chemotherapy alone (simulating zero RT dose). No prior treatments were delivered to these patients. Thirty three papers, which were published from 1990 to 2015, with comprehensive descriptions on patients, delivered treatment (chemotherapy regimen, RT prescription dose, fractionation) and response to therapy (according to WHO or RECIST guidelines [39,40]) were included in this study [2-34].

The groups RT+5-FU and RT+GEM were composed by a total of 1196 patients treated from about 1988 to 2008. RT doses, ranging from 3.6-64.8 Gy delivered in fractions of 1.2-8 Gy in 2-54 fractions, were converted to a common 2 Gy fractionation scheme using the Biological Effective Dose (BED) concept [41]. The best estimates for the delivered doses were made based on the information described in each report about compliance to treatment. Response Rate (RR), as quantified by the sum of the rate of complete and partial tumor response to therapy, was used as the endpoint of interest for the derivation of the dose-response curve. For pancreatic tumors, this endpoint follows more closely the typical sigmoidal shape of radiobiological models than the endpoint local control (given by the sum of RR and the rate of stable disease) [42].

The probability of tumor response to the delivered treatment, P, was determined assuming an additive effect between chemotherapy and RT using the expression,

$$P = P_{ch} + P_{rt}(1 - P_{ch}) \quad (1)$$

where P_{ch} and P_{rt} are the probability of response to the chemotherapy regimen and the delivered RT, respectively [43]. The probability of response to chemotherapy was calculated as the weighted mean of the RR obtained to chemotherapy delivered as monotherapy [28-31]. The Poisson-Linear-Quadratic-Time model was used to describe tumor response to RT for the groups of patients treated with RT concomitant with GEM (RT+GEM) or RT concomitant with 5-FU (RT+5-FU). The parameters of this model are: D_{50}, the dose that results in a 50% response; γ, the maximum normalized dose-response gradient; α/β, the fractionation sensitivity parameter of the Linear-quadratic model, T_{pot}, the tumor potential doubling time and T_k, the time at which repopulation begins. The parameters: α, β, γ, T_{pot} *and* T_k were derived using genetic algorithm optimization to minimize the least-square fitting error and D_{50} and α/β were calculated using the expressions described in Ferreira et al [41]. The goodness of the fit was evaluated using the Pearson χ^2-test.

3 Results

The local control rates of the patient cohorts that received RT+5-FU varied between 25% and 100%, whereas for those treated with RT+GEM it varied between 33% and 100%. The RR of the group RT+5-FU varied between 5% and 45%, whereas for the RT+GEM group it ranged from 5% to 50%. The average of RR for patients treated with chemotherapy alone with 5-FU was 7.1% and with GEM was 9% (range: 4%-15%). The RR as a function of the delivered dose for a 2 Gy fractionation schedule (EQD2) is shown Fig. 1. The values of the dose-response parameters of the Poisson-Linear-Quadratic-Time model are shown in Table 1.

Table 1. Dose-response parameters for the Poisson-Linear-Quadratic Model

Treatment	D_{50} /Gy	γ	α/β /Gy	α /Gy^{-1}	β /Gy^{-2}	T_{pot} /days	T_k /days
RT+5-FU	56.5	3.0	4.4	0.103	0.024	36.0	23.3
RT+GEM	48.3	3.0	6.4	0.134	0.021	36.0	23.3

4 Discussion

Dose-response curves for pancreatic tumors in function of BED values were first derived by Moraru et al [42] that proposed a biophysical model to describe RR to radiochemotherapy. Durante et al [43] derived dose-response models for different treatment modalities but have selected as endpoint overall survival. In this study, the Poisson-Linear-Quadratic-Time model describing RR in function of EQD2 was selected instead.

A smaller D_{50} value for concurrent radiochemotherapy with GEM compared with the D_{50} value obtained for RT+5-FU is consistent with the studies showing the higher efficacy of GEM compared to 5-FU [35,36]. During optimization the parameters α and β were derived, resulting in a α/β smaller than commonly used [42], but for RT+GEM

similar to the reported by Chapman et al [44]. A low value of α/β would explain the good local tumor response obtained with hypofractionation schedules used with Stereotactic Body RT [45].

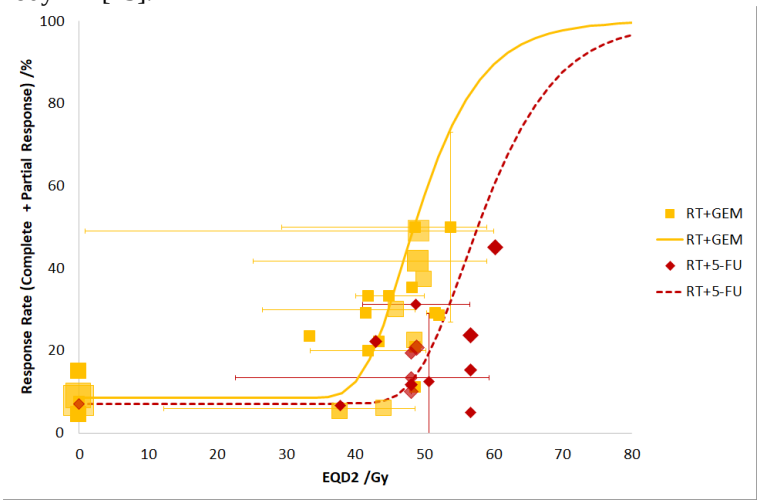

Fig. 1. Dose-response for unresectable locally advanced pancreatic tumors treated with concomitant radiochemotherapy with 5-FU or GEM. Dose-bars show the range of delivered doses and response-bars show its 95% confidence intervals reported by original authors [2-33].

Ideally, for the accurate derivation of dose-response curves, dosimetric data consisting of the delivered dose, corrected for the delivered fractions and the real overall treatment time, should be used for those patients that achieved complete or partial response. Unfortunately, discrimination between the dose delivered to patients that responded or not to the therapy was never made. Furthermore, although in each study dose prescription was uniform, the delivered dose varied due to the lack of compliance to therapy. Most authors reported a compliance to planned RT of approximately 80% but without reporting the delay in RT for each patient [2,7,23,25]. Thus, corrections for the real overall treatment time were not made. Ideally, the 3-dimensional dose-distribution should be used to assess the dose delivered to the target volume. However, with conformal RT patients with pancreatic tumors are generally irradiated with the box technique for which a good dose homogeneity in the planning target volume is obtained. Despite the uncertainties characterizing the input data, certain reasonable approximations had to be made. The result is a good model fitting as indicated by the good correlation between the dose-response curves and their association with the clinical dose-response points (Fig. 1).

5 Conclusion

The parameters for the Poisson model describing tumor response to radiochemotherapy concomitant with the 5-FU and GEM agents were derived. The determined dose-response curves indicate a good correlation between applied treatments and outcome. The

generation of large databases integrating the data of all treated patients is largely needed for the development of accurate models describing tumors, and normal tissues, to delivered therapies.

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Conflicts of interest

None.

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