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Research article

Predicting acute odynophagia during lung cancer radiotherapy using observations derived from patient-centred nursing care

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ABSTRACT

During radiotherapy, lung cancer patients commonly experience pain while swallowing (odynophagia) of food and drink. Observations from patient-centred nursing practice have been used to generate predictive models for odynophagia needing prescription pain medication during external beam lung radiotherapy for non-small cell and small-cell lung cancer. Three multivariate logistic models were evaluated in repeat cross-validation: a manual-stepwise model and two supervised machine learning models. Overall predictive performance was good. Correct classification rates ranged from 0.82 to 0.84, and areas under the receiver operator curve ranged from 0.83 to 0.85. Model sensitivity (range: 0.92–0.97) was higher than model specificity (range: 0.58–0.63). Further validation of the models in clinical context is required. A predictive model for pain medication for odynophagia prior to commencement of radiotherapy would support Radiotherapy Technologists Nurses (RTNs) in directing nursing interventions towards patients at risk.

Introduction

Chemoradiotherapy is well-established as a curative intervention for inoperable lung cancers. In external beam radiotherapy, the proximity of tumours to the esophageal tract increases the risk of damage to the mucosal lining of the esophagus. Concurrent chemotherapy [1–4] and bi-daily radiotherapy fractionation [5] are known to increase the risk of acute esophagitis. In routine clinical practice, esophagitis is not commonly assessed by objective endoscopy. Various different symptoms - such as odynophagia (painful swallowing), dysphagia (difficult swallowing), nausea, heartburn and anorexia - are widely used as clinical surrogates of esophagitis. Therefore, at mild and moderate levels of clinical severity, acute esophagitis is a highly subjective experience that varies greatly from one patient to the next.

Qualitative patient feedback in our clinic suggests that odynophagia (leading to appetite loss, dehydration and diet modification) is the dominant factor impacting on their perceived quality of life and treatment satisfaction. The objective of this investigation is to explore the incidence of low-grade acute esophagitis during lung cancer radiotherapy that manifests as patient-reported odynophagia, and hence to specifically predict when prescription pain medication may be required to manage this symptom.

Patient-centred care (PCC) is a guiding value in many clinics [6]. However, clinically meaningful PCC can only be achieved when care providers sustain systematic processes that (i) foster trust between patients and clinicians [7], (ii) enhance two-way communication about treatment effects that matter in patient lives' [8], and (iii) encourage patients to become active partners in medical decision-making [9].

Clinical scoring systems are used to objectively measure the clinical impacts of treatment-induced side-effects. However, passive observation and clinical scoring by themselves do not meet the aspirations of clinically meaningful PCC, since there is no opportunity to include a patient's own perception of the severity of side-effects or to offer them an opportunity to influence decisions about their nursing care. Sole reliance on patient self-scored outcomes may not be universally appropriate, since these

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may be modulated by social support, psychological resilience and treatment expectations.

Each radiotherapy patient in our clinic is treated by, and followed-up by, a designated Radiotherapy Technologist Nurse (RTN) team throughout their course of treatment. Teams consist of highly experienced clinical nurses that have completed an additional year of intensive training in radiotherapy. Continuity of team-based care fosters a high degree of trust needed for two-way communication with patients. Patients are encouraged to discuss any aspect of their treatment they find uncomfortable or unbearable. This qualitative information is used by RTNs to actively propose a nursing intervention before issues escalate into treatment disruptions or protocol deviations.

In a rapidly-learning healthcare system (RLHS), advanced computing uses clinical observations from routine practice to predict probable outcomes, test hypotheses and instigate improvements [10,11]. The combination of RLHS and PCC creates a virtuous cycle where routine care continuously improves and decisions (by practitioners and patients) are supported by data.

We have combined clinical, dosimetric and patient interview data to propose statistical models to predict whether a patient will require prescription medication for odynophagia during external beam radiotherapy treatment for lung cancer. Three candidate models have been developed and cross-validated. We discuss how such models can support decision-making by RTNs.

Material and methods

Outcomes registration

The outcomes were derived from semi-structured weekly in-person interviews with patients about treatment-related side-effects and how it has been impacting on his/her daily activities. A RTN actively listened if a patient made any allusion to odynophagia (for example, a persistent sore throat, pain while eating or drinking, or significantly altered dietary patterns). A hypothetical interview transcript is given in Online Supplementary Materials (Table E1). He/she probes into the severity of symptoms to assign a clinical nursing score for acute esophagitis according to department guidelines. The nursing score was derived from the Common Terminology Criteria for Adverse Events (CTCAE v4.0, see Table 1).

In keeping with PCC, the RTN also probes into medication needs from the patient's perspective. If both patient and nurse jointly arrive at a decision to begin a course of prescription medication due to odynophagia (PMO), the nursing notes will register a "PMO" event. A PMO event during radiotherapy ought to be closely correlated with the score for acute esophagitis, but these two observations are not interchangeable. Medication either prescribed prior to radiotherapy or for unrelated symptoms did not count as PMO, but the prescription medication was nonetheless noted.

PMO can only be registered either none or once during the course of radiotherapy; either a patient has not registered such an event, or an event was registered and PMO status must not be revoked even if symptoms resolve. In contrast, the esophagitis score ought to fluctuate over time. Though differences in scoring between observers cannot be ruled out, only the *maximum* score over all weeks was reported in the patient's notes.

Retrospective data screening

Electronic radiotherapy records were retrospectively screened for lung cancer treatments for either small-cell (SCLC) or non-small cell lung cancer (NSCLC). Records of patients completing their last radiotherapy fraction between January 2013 and March 2015 were reviewed. An unfiltered extract yielded 135 curative cases. Of these, 3 were excluded that had been treated for lung cancer earlier than 2013, but had since returned for additional treatment. One case was excluded because a palliative dose-fractionation had been given.

Table 1
RTN scoring guideline for acute esophagitis during radiotherapy.

Score	Description
0	No changes in the mucosa of esophagus
1	Mild swallowing pain but capable of eating a normal diet Intervention not indicated
2	Moderate swallowing pain, not capable of eating sufficiently Oral supplements and/or pain medication indicated
3	Severe swallowing pain, limiting ADL. Strong medication indicated, tube feeding, TPN and intravenous fluids required
4	Requires hospitalization and treatment
5	Death

Table 2
Characteristics of the patient cohort.

Age (years)	Median	68.0
	Range	(35–86)
Sex	Female	67 (51.1%)
	Male	64 (48.9%)
Histology	Non-small cell	101 (77.1%)
	Small cell	30 (22.9%)
Node status	Positive	73 (55.7%)
	Negative	58 (44.3%)
Chemotherapy	Concurrent	89 (67.9%)
	Sequential	32 (24.4%)
	None	8 (6.1%)
	Unspecified	2 (1.5%)
Prescribed dose	60–66 Gy	101 (77.1%)
	45 vGy	7 (5.3%)
	45 Gy (b.i.d.)	23 (17.6%)

All 131 remaining cases were used in statistical analysis. SCLC were treated once daily (45 Gy in 25 fractions) or bi-daily (45 Gy in 30 fractions), including either concommittant or sequential combination chemotherapy (carboplatinum and etoposide). NSCLC cases were prescribed doses between 60 and 66 Gy in daily 2 Gy fractions, with either concommittant or sequential combination chemotherapy (carboplatinum and vinorelbine). However, eight NSCLC patients (i.e. only 6% of the cohort) were not given any chemotherapy (see Table 2). Hence, there were insufficient frequency of events to stratify the effect of no chemotherapy.

Case reports were compiled in SurveyXact (v7.1, Ramboell Consulting, Aarhus, Denmark) using information in nursing notes, doctors notes and hospital electronic journals. SurveyXact forms were linked with treatment planning system data (Oncentra External Beam v4.3, Elekta AB, Stockholm, Sweden) and oncology information system data (MosaiQ v2.50, Elekta AB, Stockholm, Sweden). Data merging, pre-processing and statistical modelling were carried out in *R* (v3.3). Details specific to data processing are provided in supplementary materials (Table E2).

As a surrogate for esophageal exposure, the as-approved treatment plans were used. All patients were treated as a single-phase plan; in certain cases, anatomical changes in the vicinity of the tumour detected mid-treatment necessitated some combination of either re-contouring, re-simulation or re-planning. Therefore, the beam arrangement in subsequent plans was assumed to be only a minor perturbation from the initial plan. Where multiple radiotherapy treatment plans per patient were located, a consistent arbitration rule was thus applied - the cumulative dose-volume histogram (cDVH) from the treatment plan delivered on the majority of the first 15 fractions was used. In all but one case,

the selected treatment plan was chronologically the first plan delivered to the patient. Esophagus delineations were reviewed and, if missing, were retrospectively delineated by a senior radiation oncologist.

Theory/calculation

Scaling to equivalent dose

Due to differences in the dose/fractionation schedules used for NSCLC and SCLC, individual dose bins in the cumulative dose-volume histograms (cDVH) of the esophagus from the planning system was re-scaled to radiobiologically-equivalent once-daily 2 Gy doses (EQD_2) using a linear-quadratic model:

$$EQD_{2Gy} = n_f \cdot d_i \cdot \left[\frac{1 + (\beta/\alpha) \cdot d_i}{1 + (\beta/\alpha) \cdot 2}\right] - R_p \cdot max[0; (T_{tot} - T_k)] \quad (1)$$

where d_i, the absorbed dose per fraction in the i-th bin of the cDVH, such that $i = 1 \ldots N$ such that N is the integer number of dose bins; n_f, the integer number of fractions; (β/α), the inverse of the alpha-beta ratio for radiobiological response; T_{tot}, the integer number of days between the first and last fractions of radiotherapy, and finally T_k, the onset time (i.e. "kick-off") from the start of radiotherapy to the commencement of cell proliferation. For bi-daily fractionation, the effect of incomplete cellular repair calculated using the Dale formalism for incomplete repair between fractions [12] assuming fractions at least 6 h apart, was found to be negligible.

In Eq. (1), the (β/α) was assumed to be 0.1 for early reactions anywhere in the upper gastro-intestinal tract [13]. The proliferation rate constant in esophageal mucosa was assumed to be the same as for early-reacting head-and-neck mucosa ($R_p = 0.8$) commencing 7 days ($T_k = 7$) after the start of radiotherapy [13].

Statistical modelling and machine learning

Univariate logistic (UL) and multivariate logistic (ML) regression of clinical parameters against PMO was performed. No specific correction was made for multiple hypothesis testing in the UL analysis. Forward stepwise parameter selection in ML regression was guided by the Akaike Information Criterion (AIC). If different parameters resulted in the same AIC, the more clinically robust parameter was selected. For example, positive node status would be preferred over Gross Tumour Volume (GTV), since the latter would be subject to inter-observer variation due to manual delineation.

In the machine-learned classifier domain, Lasso & Elastic-Net Regularized Generalized Linear Models (*glmnet*) [14] leads to parsimonious models with few input parameters. Support Vector Machines (*svm*) [15] with radial kernals perform classification by re-mapping the problem into a hyperspace of many different combinations of the input parameters, such that segregation of PMO from non-PMO is as wide as possible.

ML, *glmnet* and *svm* models were trained on all 131 patient cases. To reduce the risk of over-fitting, every training run involved randomized splitting of the data for 10-fold cross-validation with 10 repetitions per random fold. Training of the ML and *glmnet* models were optimized for maximum classification accuracy over all folds and all repetitions. Training of the *svm* model was optimized for maximum area under the curve (AUC) in its receiver-operator characteristic (ROC) curve.

Approvals for conduct of study

This retrospective study was strictly register-based and utilizes only routine clinical treatment information, and had been approved by the Danish Data Protection Agency as an acceptable use of personal data for quality development. The study complies with hospital policies based on the Helsinki II Declaration, Good Clinical Practice guidelines and other relevant research guidelines enforced in Denmark. In accordance with Danish law, this study was not required to be submitted for review by the Health Research Ethics committees for Region South Denmark.

Results

Descriptive analysis of the data showed that PMO events are common; it was noted in 88 out of 131 patients (67%). In 29 patients with esophagitis score of 0, only 3 (10%) of them registered a PMO event. For clinical esophagitis score 1, 74 out of 88 patients registered PMO (84%). All of the 11 patients with clinical esophagitis score 2 registered a PMO event (100%). This has been summarised in Table 3.

Single-parameter logistic regression against PMO did not support any statistically significant association with baseline observations such as gender, BMI or pre-existing pain medication prior to radiotherapy. Our data did not support an association between PMO and type of chemotherapy. There were potentially positive associations between PMO with centrally-located tumours, positive nodal involvement and age at commencement of radiotherapy (see Table 4). Univariate tests against dosimetric parameters derived from radiobiologically-adjusted (EQD_2) cDVH metrics were suggestive of a strongly dose-dependent response to the dose estimated in the highest-dose 1 cc.

The predictive performance metrics for each model is shown in Table 5. ML regression had the fewest input parameters (3), whereas *svm* incorporated all 30 available parameters. We were able to strike a compromise with *glmnet* between number of input parameters and predictive performance, resulting in a model with similar predictive performance using 8 input parameters. In each model, the correct-classification rate (combined true positives and true negatives) in cross-validation was over 82%. In all models, the 95% confidence interval (from repeated cross-validation) for the estimated predictive accuracy was above the no-information-rate of 67%. The AUC metrics ranged between 0.83 and 0.85.

Sensitivity, specificity, predictive values and likelihood ratios are also reported in Table 5. Generally, the sensitivity of the models were high, between 0.92 and 0.97. Overall specificity was quite low, in the range 0.58–0.63. Positive (PPV) and negative predictive values (NPV) across the models exceeded 79%. Positive likelihood ratios ranged from 2.3 to 2.5, and negative likelihood ratios ranged from 0.05 to 0.13.

Discussion

Interviews by RTNs were combined with electronic medical records and radiotherapy dosimetry data to produce an enriched data set, from which we developed prediction models for prescription pain medication due to odynophagia.

Decision support tools tailored for use by RTNs are required, so that they can pro-actively tailor interventions towards the risk profile in each patient. By documenting nursing interventions and associated patient outcomes, it would be possible to refine and improve the predictive performance of such models. This instigates the virtuous cycle of continuous improvement in quality of patient care by combining PCC and RLHC.

By establishing a strong bond of trust between the patient and their RTN team, a shared consultation space was created where the patient felt safe and secure. The patients were then able to describe the symptoms of swallowing pain during drinking and eating. The patients' descriptions and their qualitative feedback showed that

Table 3
Distribution of PMO event among patients with different grades of clinically (nurse) scored acute esophagitis during their course of radiotherapy.

Acute esophagitis score	Risk of PMO event
Grade 0	3/29 (10%)
Grade 1	74/88 (84%)
Grade 2	11/11 (100%)
Grade 3+	0/0 (–)

Table 4
Single-parameter logistic regression against PMO. Only $p < 0.05$ are shown. The annotations correspond to: $(***)$ $p < 0.001$; $(**)$ $p < 0.01$; $(*)$ $p < 0.05$. The dose-volume histogram annotation V_{xGy} denotes the volume of esophagus receiving a dose of at least x Gy, and the annotation D_{xcc} denotes the dose in the hottest x cubic centimetres of the esophagus.

Parameter	p-value
Tumor located centrally in thorax	***
Positive node involvement	***
Age when commencing radiotherapy	**
Overall length of treatment course	*
Sum volume of nodal GTVs (4D CT)	*
Sum volume of nodal GTVs (3D CT)	*
Esophageal dose-volume indices:	
V_{5Gy}	***
V_{10Gy}	***
V_{15Gy}	***
V_{25Gy}	***
V_{30Gy}	***
D_{1cc}	***
D_{2cc}	***
D_{5cc}	***
Maximum point dose	***
Mean dose	**
Median dose	**

Table 5
Predictive performance of models for PMO.

	ML regression	*glmnet*	*svm*
No-information-rate	0.67	0.67	0.67
Number of parameters	3	8	30
Correct classification rate	0.82	0.84	0.83
(95% confidence interval)	(0.75–0.88)	(0.77–0.90)	(0.76–0.89)
Kappa agreement rate	0.58	0.60	0.60
Area under curve (AUC)	0.83	0.85	0.85
Sensitivity	0.92	0.97	0.93
Specificity	0.63	0.58	0.63
Pos. predictive value (PPV)	0.83	0.82	0.84
Neg. predictive value (NPV)	0.79	0.89	0.82
Pos. likelihood ratio (LR+)	2.5	2.3	2.5
Neg. likelihood ratio (LR−)	0.13	0.05	0.11

RTN teams were able to use these interview sessions to quickly pinpoint symptoms of immediate concern to the patient, and focus nursing care towards managing those concerns.

As expected, the correlation between PMO rates and nurse-scored esophageal toxicity was strongly positive. The grade-stratified risk of PMO event increased monotonically from 10% in patients scoring 0 up to 100% in patients scoring 2.

However, the relationship of PMO with clinically-assessed toxicities cannot be strictly deterministic. The patient-reported outcome of pain during swallowing may be associated with either dysphagia [16] (e.g. difficult swallowing, or feeling a "lump in the throat"), or with esophagitis [1–4] (e.g. acid reflux or burning sensation in the throat or within the chest). The correspondence is unlikely to be exact because a sticking sensation in the throat need not always be accompanied by pain, and esophageal irritation due to acid reflux does not always require prescription pain medication to address. We further hypothesise that patient tolerance of swallowing pain is being modulated by their level of social support, their personal levels of resilience, and pre-conceptions they harbour about radiotherapy treatment. At time of writing, we know of no other prediction modelling study that focusses on a specific patient-reported symptom of radiation treatment that requires prescription pain medication.

A predictive model for odynophagia prior to commencement of the first fraction of radiotherapy would allow nurses to target appropriate nursing interventions towards patients at elevated risk. Given a pre-test baseline of 67%, a positive result from any one of the above models implies approximately 80% probability of the patient having a PMO event during radiotherapy. Conversely, a negative result implies about 20% chance of PMO event during radiotherapy. If RTNs are aware that a particular patient is at high risk, they may be able to commence additional counselling, dietary modification advice and/or adjust expectations prior to start of radiotherapy.

If the intended nursing intervention leads to other side-effects or are relatively expensive to offer, it would be desirable to target such interventions towards patients who are most at risk. This approach opens a way forward towards shared decision making, since patients and nurses may (using a prediction model and the known side-effects of a proposed intervention) discuss the risk trade-offs between pre-emptively starting prescription pain medication before the first fraction of radiotherapy, or else to delay pain medication as long as possible.

The ML regression-based model would be simple for RTNs to apply, with minimal technical support. However, manually-constructed models are labour-intensive to maintain and to subsequently update. Updates to the model requires suitably competent staff to process data and update the models at regular time intervals. In contrast, machine learning models such as the *glmnet* and *svm* can be set up as automated scripts to execute at predetermined timepoints on a given database, and can therefore update models efficiently. However, the use of complex mathematical models at the point of nursing care needs to be carefully developed and adequately supported by user-friendly interfaces. One important concern for any predictive models is the degree to which their use integrates seamlessly into the routine nursing workflow.

While the performance of the models is currently satisfactory, further validation in a prospectively enrolled cohort would be highly desirable. In order to train the models on the largest data set possible, a small external validation subset was not partitioned from the available data. However, the use of multiple cut-off testing when tuning the model may lead to increased risk of Type I error (false discovery rate) [17]. Therefore, clinical validation in an independently recruited set of patients would be necessary prior to clinical implementation.

Furthermore, the current models must assume that the esophageal dosimetric indices of interest are the same as those derived in one-time radiotherapy treatment planning. It is well known that the actual esophagus and other adjacent organs can move and deform significantly day by day, as well as over several weeks of radiotherapy. Presently, no attempt at dose summation or anatomically-based dose tracking has been included in the modelling. This would be presently difficult to perform, as deformable image co-registration and dose computation on daily cone-beam computed tomography is not yet of sufficient technical maturity for daily use.

Conclusion

A radiotherapy nursing workflow has been defined that respects the ideals of PCC. Observational data from semi-structured nursing interviews has been merged with electronic journal entries and

radiotherapy treatment planning data. Three predictive models have been assessed for pain medication due to odynophagia during curative external beam radiotherapy of lung cancers. Models perform well in cross-validation, and further independent validation using recent clinical data will be required. Statistical models that capture implicit clinical knowledge among nurses could in future be deployed to predict (or reduce reliance on) pain medication for odynophagia *prior to the start of radiotherapy* with potential improvements in quality of life for patients receiving lung radiotherapy.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tipsro.2018.01.002.

References

[1] O'Rourke N, Roqué i Figuls M, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev 2010;6:CD002140.
[2] Ahn S-J, Kahn D, Zhou S, Yu X, Shafman TD, Marks LB. Dosimetric and clinical predictors for radiation-induced esophageal injury. Int J Radiat Oncol Biol Phys 2005;61:335–47.
[3] Belderbos J, Heemsbergen W, Hoogeman M, Pengel K, Rossi M, Lebesque J. Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy. Radiother Oncol 2005;75:157–64.
[4] De Ruyck K, Sabbe N, Oberije C, Vandecasteele K, Thas O, De Ruysscher D, et al. Development of a multicomponent prediction model for acute esophagitis in lung cancer patients receiving chemoradiotherapy. Int J Radiat Oncol Biol Phys 2011;81:537–44.
[5] Turrisi 3rd A, Kim K, Blum R, Sause W, Livingstone R, Komaki R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;340:265–71.
[6] Ekman I, Swedberg K, Taft C, Lindseth A, Norberg A, Brink E, et al. Person-centered care ready for prime time. Euro J Cardiovasc Nurs 2011;10 (4):248–51.
[7] Dieppe P, Rafferty A, Kitson A. The clinical encounter the focal point of patient-centred care. Health Expect 2002;5:279–81.
[8] Kitson A, Marshall A, Bassett K, Zeitz K. What are the core elements of patient-centred care? A narrative review and synthesis of the literature from health policy, medicine and nursing. J Adv Nurs 2013;69:4–15.
[9] Epstein R, Street Jr R. The values and value of patient-centred care. Ann Family Med 2011;9:100–3.
[10] Abernethy A, Etheredge L, Ganz P, Wallace P, German R, Neti C, et al. Rapid-learning system for cancer care. J Clin Oncol 2010;28:4268–74.
[11] Lambin P, Roelofs E, Reymen B, Velazquez E, Buijsen J, Zegers C, et al. Rapid learning health care in oncology - an approach towards decision support systems enabling customised radiotherapy. Radiother Oncol 2013;109:159–64.
[12] Dale R. The application of the linear-quadratic model to fractionated radiotherapy when there is incomplete normal tissue recovery between fractions, and possible implications for treatments involving multiple fractions per day. Brit J Radiol 1986;59:919–27.
[13] Fenwick J, Nahum A, Malik Z, Eswart C, Hatton M, Laurence V, et al. Escalation and intensification of radiotherapy for stage iii non-small cell lung cancer: opportunities for treatment improvement. Clin Oncol 2009;21:343–60.
[14] Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. J Stat Software 2010;33(1):1–22. https://doi.org/10.18637/jss.v033.i01. , <https://www.jstatsoft.org/index.php/jss/article/view/v033i01>.
[15] Karatzoglou A, Smola A, Hornik K, Zeileis A. kernlab – an S4 package for kernel methods in R. J Stat Software 2004;11(9):1–20. , <http://www.jstatsoft.org/v11/i09/>.
[16] Dehing-Oberije C, De Ruysscher D, Petit S, Van Meerbeeck J, Vandecasteele K, De Neve W, et al. Development, external validation and clinical usefulness of a practical prediction model for radiation-induced dysphagia in lung cancer patients. Radiother Oncol 2010;97:455–61.
[17] Altman D, Lausen B, Sauerbrei W, Schumacher M. Dangers of using optimal cutpoints in the evaluation of prognostic factors. J Natl Cancer Inst 1994;86:829–35.