

A Rule-based Model for Local and Regional Tumor Spread

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Abstract

Prediction of microscopic spread of tumor cells is becoming critically important in the decision making process in planning radiation therapy for cancer. Until recently, radiation treatment of head and neck cancer has been conservative, treating large regions to insure eradication of disease. However, if it is known that regional spread is confined, a more focused treatment can be considered, with the payoff of reducing or eliminating morbidity due to irradiating healthy tissue in the vicinity of node groups. Knowledge about the occurrence of micrometastases comes mainly from pathology reports in connection with surgery. As the data accrue, it will be possible and necessary to represent this knowledge in a symbolic computational model. Our work reports on the feasibility of modeling this knowledge using published data.

INTRODUCTION

Radiation oncology has played a prominent role in the management of head and neck cancers. Radiation oncologists have used surgically-derived data to design traditional radiotherapy fields that treat the obvious primary tumor and electively treat adjacent lymph node levels felt to be at significant risk for subclinical disease. Given the limitations of traditional technology and radiation delivery systems, these fields have historically been comprehensive in nature since highly selective targeting of individual lymph node levels and exclusion of others was impossible in many clinical situations. This technological limitation is being overcome, and therefore radiation oncologists are beginning to reevaluate the available literature in order to rationally design highly selective treatment fields.

One such technique, intensity-modulated radiation therapy (IMRT),¹ shows great promise. This technique achieves a high dose to a defined target region with a sharp falloff at the boundary. Figure 1 shows a cross sectional view of a treatment plan using IMRT for a clival meningioma. The tumor is in a region between the optic chiasm and the brain stem, and has an

elongated shape unsuitable for conventional radiotherapy. Achieving a sharp falloff at the boundary results in lower dose to the surrounding critical organs, with consequent reduced morbidity, or alternately allows a higher dose to the tumor, giving better local control (destruction of all the tumor cells).

This of course assumes that the radiation oncologist is able to precisely delineate (for each patient individually) the target volume, i.e., the volume to irradiate.² In fact, there is no computational technique at present for doing this. The radiation oncologist draws outlines representing his/her best estimate of how far the tumor has spread microscopically from the primary site. This depends on the size of the tumor, the type of cells, and most critically the surrounding anatomy. Tumor cells migrate along lymph drainages, and along nerves in some cases. They cannot be made visible with any imaging techniques known today.

Pathology findings following surgery have been reported in the literature, usually to address specific questions such as whether or not to include a specific node group in the target volume. Generally tumor spread largely follows anatomic structure and biologic principles, but no computational models for this have been proposed. As tumors become larger and time elapses, the probability of more distant node groups being positive for microscopic spread increases.

The goal of our work is to propose and validate a computational model of local and regional disease spread based on production rules, representing clinical data, anatomic knowledge and clinical judgement. The work reported here is the first step in this direction. A truly powerful system implementing the model would also need to be able to apply image processing techniques to compute the boundaries of the selected nodal regions in a patient specific way. Work is also in progress to solve this problem and will be reported elsewhere.

The model we describe is being developed as a component of the Prism radiation therapy planning system,³ developed and in clinical use at the University

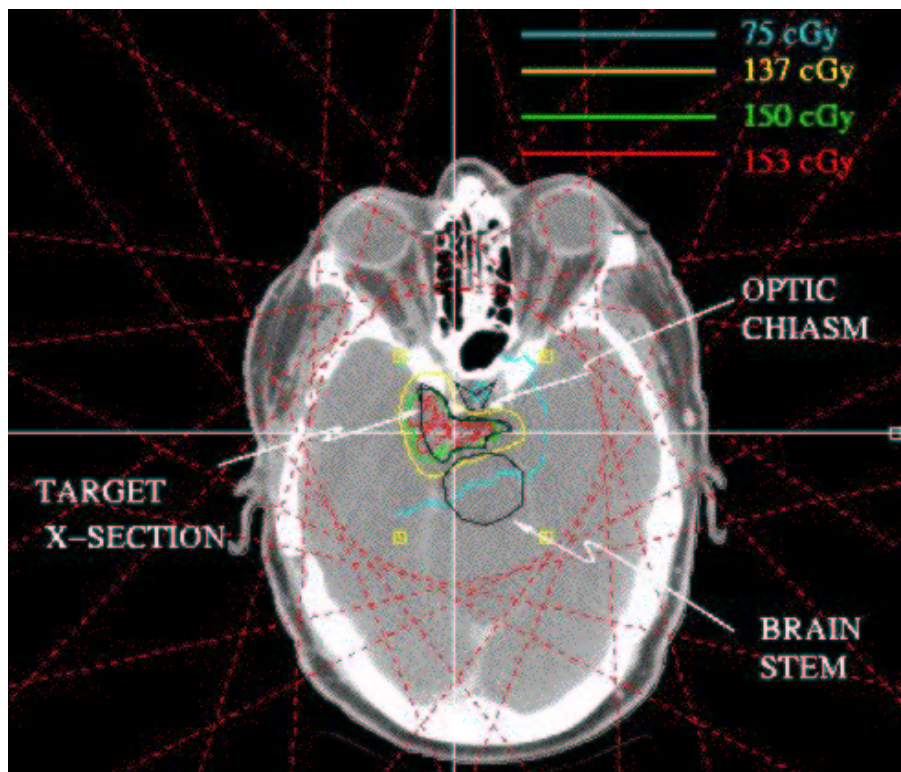


Figure 1: A cross-sectional view of an IMRT radiation treatment plan. The nine treatment fields are each modulated across their apertures to produce the very tailored dose distribution shown, which avoids the brain stem, the optic chiasm and as much as possible of the rest of the surrounding brain tissue.

of Washington Cancer Center. This will give us the opportunity in the future to test the model in a clinical environment, and demonstrate how it can be deployed clinically, so that it can have a real impact on practice.

TUMOR SITES AND NODAL REGIONS

Head and neck cancers are a heterogeneous collection of malignancies arising in multiple anatomic subsites, each with unique clinical, pathological, and prognostic features. The vast majority of these cancers are squamous cell carcinomas that originate in the normal mucosal lining located throughout the head and neck. As these squamous cancers enlarge, they tend to spread from primary location to nearby regional lymph nodes in a predictable sequence. Curative treatment of these cancers, therefore, has historically required attention to the draining regional lymph nodes that could harbor microscopic disease.

The development of standardized surgical approaches to the neck (e.g., radical neck dissection, selective neck dissection) has paralleled development of standardized nomenclature for the various nodal regions (“levels”) in the neck.^{4, 5} (See Table 1.)

In addition, several published series of surgically-

Table 1: Current classification of cervical lymph nodes

Level Ia	Submental group
Level Ib	Submandibular group
Level II	Upper jugular group
Level III	Middle jugular group
Level IV	Lower jugular group
Level V	Posterior triangle group

treated patients have provided valuable pathologic data allowing statistical estimation of the risk for subclinical nodal involvement according to these neck subdivisions.^{6, 7, 8, 9} The example data shown in Table 2 are adapted from Shah, et. al.⁹

RULES FROM PUBLISHED DATA

We initially intended to generate production rules based solely upon published statistics of metastatic tumor spread in the head and neck. The literature contains a number of studies examining the probability of neck metastases for various primary sites. The majority of these studies publish overall probabilities of

Table 2: Prevalence of subclinical lymph node involvement according to tumor site

Nodal Level	Tumor location				
	Oral tongue	Floor of mouth	Alveolar ridge	Retromolar trigone	Buccal mucosa
I	14%	16%	27%	19%	44%
II	19%	12%	21%	12%	11%
III	16%	7%	6%	6%	0%
IV	3%	2%	4%	6%	0%
V	0%	0%	2%	0%	0%

metastasis broken down by the T stage of primary tumor. Unfortunately, few studies report the levels of the neck where metastases occur.^{7, 10, 11} Several reasons account for the lack of specific data on the location of neck metastases. Typically, these studies use the pathologic specimens from a series of neck dissections. These pathologic specimens do not necessarily contain the landmarks that allow the surgical pathologist to determine the anatomic location of lymph nodes within the specimen. Additionally, in the past several decades, selective neck dissections that do not remove all of the lymphatic contents of the neck have become the standard of care for a variety of lower stage tumors. In these cases, the presence of micro-metastases in the undissected areas can only be inferred from the incidence of treatment failures in these areas.

Unfortunately for our purposes, most of the studies that break down metastases by location in the neck do not report these results by the T and N stage of the primary tumor. To create production rules that specify which levels of the neck to treat for a specific TNM stage primary tumor, we need probabilities for the presence of tumor in each level of the neck for each TNM stage. Although this information was not reported in these studies, we inferred conservative estimates of these probabilities from the published data. This was accomplished by utilizing the reported overall percentage of patients at each T and N stage and the reported overall probabilities of tumor metastasis at each neck level (independent of T stage). To calculate an upper limit of probability, we made use of the evidence that a more advanced stage squamous cell carcinoma (higher T and N stage) is more likely to exhibit regional metastases than a lower stage SCCA of the same primary site. For each primary site and each level of the neck, the number of positive metastases was reported. For each T and N stage, we calculated the probability of metastasis for each neck level by dividing the number of positive metastases at that level by the sum of the patients with the given T and N stage and all patients with a higher T and N stage. This method likely overestimates the probability of metas-

tasis at a given T and N stage. This is due to fact that calculating the metastatic probability in the manner assumes that all metastases occur within the patients with at least the given T and N stage, and that the distribution of the metastases within this group of patients is uniform. In reality the distribution of metastases is probably skewed towards more advanced T and N stages, but is unlikely to be skewed towards less advanced T and N stages. So by assuming a uniform distribution, we can estimate the maximum probability that a given T and N stage would metastasize to a specific level of the neck.

Additional estimates can be formulated in a similar manner, from studies that report an overall incidence of metastasis by specific T and/or N stage. For each T and N stage, the number of overall metastases can be assigned to each level of the neck. Clearly, this also is overestimating the probability of individual metastases, but by combining the results of multiple studies and choosing the lowest “upper margin” of probability, a more accurate estimate can be achieved. However, additional factors complicate the effort to combine the results of different studies. In addition to factors mentioned previously, other factors include the type of study (prospective vs. retrospective), the number of patients included, and the degree of specificity used to classify the primary tumor site.

We collected data from several large prospective and retrospective studies, limiting our focus initially to squamous cell carcinomas of the oral cavity, oropharynx, hypopharynx and larynx. Not surprisingly, there tended to be a trade-off between specific primary tumor sites and large sample size. We used the most specific primary tumor site possible, given the available data in each study. When data were available on the same primary site from different studies, we utilized the results for the more specific primary site, as long as sufficient samples ($n \geq 10$) were reported. When the sample size was small, we used data from more general primary sites. In practice, no single study contained sufficient data to compute complete probabilities for all primary sites. Rather a subjective com-

pilation of the data was used to determine treatment recommendations. A shortcoming of most of the studies was the lack of information on contralateral metastases.

We ran our calculations with treatment thresholds of 15%, 10% and 5%. That is, if the preponderance of the data indicated a metastatic probability of 15% or greater (or 10% or 5%), we would generate a rule to treat that level of the neck.

ANATOMIC MODEL OF THE LYMPHATIC DRAINAGE OF THE NECK

An advantage in treating squamous cell carcinoma of the head and neck is the relatively constant and orderly progression of lymph node metastases in the untreated neck. The primary and secondary lymphatic drainage of the various primary sites has been well described. We sought to correlate the literature data on nodal metastases with the anatomic model of lymphatic drainage, in order to support the literature data when available, and augment areas where the literature is lacking. Using the Foundational Model of Anatomy (FM) developed by the University of Washington Structural Informatics Group,¹² we identified all references to lymph nodes of the head and neck. The majority of nodal groups described in the literature were included in the FM, with the notable absence of a specific reference to the deep middle cervical nodes that lie in level III of the neck. Moreover, the FM lacks the anatomic relationship between primary sites of the head and neck and the nodal groups with drain these sites. These relationships were constructed from the anatomic literature to be used in the decision hierarchy.

SURVEY OF EXPERT PHYSICIANS

As noted above, the published literature allows us to estimate an upper limit to the probability of regional neck metastasis. This upper limit is probably more accurate for more advanced disease, since the distribution of metastasis is likely skewed towards more advanced primary tumors. For less advanced disease this method may greatly overestimate metastatic potential. These less advanced tumors represent an area where IMRT can provide improved outcomes, so determining a more accurate estimation of which neck levels require treatment is an important goal. Radiation oncologists and head and neck surgeons make educated guesses of these probabilities when treating patients with head and neck cancer. We surveyed four radiation oncologists in both an academic and private practice setting. In addition we surveyed three head and neck surgeons, all of whom practice in an academic setting. Each has significant experience treating head

and neck cancer patients. These experts were asked to identify which lymph node levels (ipsilateral Ia-V, contralateral Ia-V) they would include in a clinical target volume for six hypothetical head and neck cancer patients desiring treatment with definitive conformal radiotherapy. The six selected cases used in the survey are listed in Table 3 along with the number of experts who recommended treatment of each lymph node region. All cases were presumed to be squamous cell carcinomas.

None of the six hypothetical cases produced complete agreement among the experts as to which cervical lymph node levels should be included in the clinical target volume. The agreement was greater for certain tumor sites and certain node groups. There was no discernable difference between the two types of physicians (radiation oncologists and surgeons).

RESULTS AND DISCUSSION

We used the results of the expert survey to test the literature and our anatomic based model. We used the five hypothetical cases relating to tumors of the oral cavity, oropharynx, and hypopharynx, since rules for these systems had been developed. Scores were obtained by calculating the percentage of expert opinions that agreed with the system's recommendation in either a decision to treat or not to treat. Scores were calculated from rules generated using treatment thresholds of 15%, 10%, and 5% chance of metastasis at a given neck level. Using a threshold of 15% the agreement between the system and the experts was 66.3%. An agreement rate of 68% was obtained using a threshold of 10%, and a rate of 74.3% was obtained using a threshold of 5%. We also calculated the agreement between each expert and the others, in order to estimate the degree to which the experts agree on treatment recommendations. The agreement rate of an individual expert, compared to the others, ranged from 79-81%, with an overall agreement rate of 80%. Not surprisingly, the 10% and 15% thresholds erred on the side of under-treating disease for which the experts recommended treatment, while the 5% threshold erred on the side of over-treating disease for which the experts did not recommend treatment. From these results it appears that the experts' threshold for treatment lies in the range of 5-10% probability of metastatic disease.

The results show that even with the limitations inherent in published data, it is feasible to create a rule-based system for automatically determining which nodal regions should be included in the treatment volume. However, to develop a really accurate system, additional data will be required. Further, the type of analysis and reporting of pathologic findings will need to change. The model we are trying to develop requires

Table 3: Results of the expert survey

Description of Hypothetical cases	Number of experts including lymph node region											
	ipsilateral						contralateral					
	Ia	Ib	II	III	IV	V	Ia	Ib	II	III	IV	V
T1N0M0 L tonsil		1	4	4								
T2N0M0 R base of tongue	1	3	5	5	5	3	1	2	4	4	3	2
T3N0M0 L floor of mouth	4	5	5	5	5	3	4	5	5	2		
T1N0M0 L nasopharynx	1	2	5	5	4	5	1	2	5	5	3	5
T2N0M0 R pyriform sinus			5	5	5	3			5	5	5	2
T2N0M0 L lateral oral tongue	3	5	5	5	5		2	4	4	4	2	

a change in the kinds of questions to be asked. Instead of generalized “Should we treat level IV for base of tongue tumors”, the data must be accumulated routinely with specificity of staging and specimen origin. This kind of pathologic study is now routine at the University of Washington Medical Center, and will allow more refinement in the system as it is built.

In this study, the hierarchical application of rules was done by hand. In an actual system, a hierarchical representation of the tumor primary sites and a conflict resolution strategy will have to be coded as part of the design.

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