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EDITORIAL

Artificial intelligence in dentomaxillofacial radiology

Seyide Tugce Gokdeniz, Kıvanç Kamburoğlu

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Abstract

Artificial intelligence (AI) has the potential to revolutionize healthcare and dentistry. Recently, there has been much interest in the development of AI applications. Dentomaxillofacial radiology (DMFR) is within the scope of these applications due to its compatibility with image processing methods. Classification and segmentation of teeth, automatic marking of anatomical structures and cephalometric analysis, determination of early dental diseases, gingival, periodontal diseases and evaluation of risk groups, diagnosis of certain diseases, such as; osteoporosis that can be detected in jaw radiographs are among studies conducted by using radiological images. Further research in the field of AI will make great contributions to DMFR. We aim to discuss most recent AI-based studies in the field of DMFR.

Key Words: Artificial intelligence; Diagnostic imaging; Radiology; Dentistry

Core Tip: Scientists are enthusiastic about conducting artificial intelligence (AI) research related to dentomaxillofacial radiology (DMFR). Image and patient recognition are important in DMFR, however initial investment costs are still high and misdiagnosis may occur in real clinical situations. Up until now, DMFR related AI studies revealed successful results to some extent, however human physiological system is so complex that AI can be a supplementary method but not a substitution for human knowledge, capability and decision-making ability.

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INTRODUCTION

In recent times, technical developments and innovation have become integral parts of clinical dentistry. Owing to recent developments in the field of artificial intelligence (AI), significant improvements may be expected in dentistry and dentomaxillofacial radiology (DMFR). AI is defined as the way, method, tool, and algorithm, that is developed for the intelligent solution of the issues encountered with computer application of intelligent thinking. They contain elements which are able to imitate human thinking, understanding, comprehension, interpretation and learning characteristics utilized for problem solving[1]. Numerous studies have been carried out in order to find solutions that utilize the latest technology to solve dental field-related issues. These studies are comprised of a wide range of objectives, including the diagnosis of caries; assessment of various pathologies; orthodontic treatment of crowded teeth and dental implant placement *via* robotic surgery[2-5]. In DMFR studies, this technology has come to the forefront due to its compatibility with image processing methods. Current topical examples of studies conducted on radiological images are: Classification and segmentation of teeth; automatic marking of anatomical structures and cephalometric analysis; early detection of dental diseases; gingival-periodontal diseases and evaluation of risk groups and the diagnosis of certain diseases such as osteoporosis that can be detected in jaw radiographs[6]. In dental radiology there are both theoretical and practical application examples of these specific tasks. The output gained from artificial learning is expected to reduce the daily workload of physicians as well as the rate of both false diagnosis and underdiagnosis in dental practice.

According to the radiological diagnosis tool used, we aim to present the current studies in the field of DMFR under two main headings. Current AI studies in the field of DMFR are given in Figure 1. The main study topics in DMFR related to AI are given in Table 1.

Some of the current AI studies using panoramic radiography devices

The most widely used radiological diagnostic tool in dentistry is the panoramic radiograph. It provides two-dimensional image and related information regarding major mandibular and maxillary jaw bones, all existing teeth and surrounding supporting tissues. Two-dimensional imaging of this region, which has a complex anatomy, causes superposition of various tissues on each other. Therefore, it is possible that panoramic radiographs can be interpreted incorrectly or incompletely in certain cases. Critical assessment of dental images is an essential portion of the diagnostic procedure in daily clinical scenarios. General evaluation by a specialist is based on tooth detection and numbering[7]. A study verified the assumption that a convolutional neural network-CNN-based method could be skilled to analyze and score tooth on panoramic images for automated dental charting objectives. The suggested method targeted at assisting dentists during their diagnostic procedures. The system's performance level was found to be similar to the specialists' level, which meant that the radiology specialist could use the finding gained from the technique for automated charting when solely assessment and subtle adjustments were necessary as an alternative to manual data insertion[7].

Several different studies are published on the automatic detection of odontogenic cysts and tumors[8-10]. Odontogenic cysts and tumors do not demonstrate their distinctive radiographic features until they extend to a significant dimension. The early radiographic findings of odontogenic cysts and tumors are so similar that even well trained DMFR experts cannot always accurately conduct their diagnosis. In addition, they may not reveal symptoms in advanced levels[11,12]. Because of such characteristics of odontogenic cysts and tumors, commonly observed cysts such as dentigerous cysts and odontogenic keratocytes may threaten the patient's quality of life if they are large or subsequently cause pathological fractures[13,14]. However, *You Only Look Once* (*YOLO*)-a state-of-the-art, real-time object detection system could not be only responsible for the wrong negative diagnosis in one research, which consisted of radiologically indeterminate initial pathologies and maxillary entities that even trained clinicians find difficult to accurately diagnose. As noted, some pathologies in the maxilla are hindered by low bone density and several related anatomical structures that cross with the superpositions of the panoramic image. Odontogenic keratocytes on the maxilla were not detected by both YOLO and two-thirds of clinicians, including experts and general practitioners. Surprisingly, however, there were few instances where YOLO diagnosed and accurately distinguished pathologies that clinicians could not detect[15]. The CNN YOLO detector demonstrated diagnostic effectiveness at least comparable to that of trained dentists in assessing odontogenic cysts and tumors[15]. A number of components affecting clinician ability need to be assessed in future research. It is possible that implementation of CNNs in oral and maxillofacial diagnostic imaging may reveal favorable results for clinicians[15].

Ameloblastomas and keratocystic odontogenic tumors (KCOTs) are among the most commonly observed odontogenic tumors of the jaws. Preoperative definitive detection of these lesions may help dental surgeons in treatment planning[16,17]. In another study, a CNN was created for the evaluation of ameloblastomas and KCOTs[3]. The accuracy of the CNN developed in this study was close to the accuracy of dental experts in detecting ameloblastoma and KCOTs. CNN can help reduce the workload of oral and maxillofacial surgeons by detecting ameloblastomas and KCOTs in a very short time. More research needs to be done in order to clarify and define CNN before it may be widely used in diagnostic imaging purposes[3].

Table 1 Main study topics in dentomaxillofacial radiology related to artificial intelligence

No.	Main study topics
1	Localization/measurement of cephalometric landmarks
2	Diagnosis of osteoporosis
3	Classification of the maxillofacial cysts and/or tumors
4	Identification of alveolar bone resorption
5	Classification of periapical lesions
6	Diagnosis of multiple dental diseases
7	Classification of tooth types
8	Detection of dental caries
9	Classification of the stage of the lower third molar

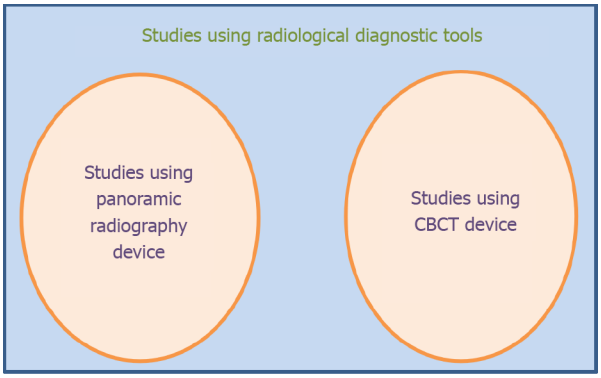

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Figure 1 Current artificial intelligence studies in the field of dentomaxillofacial radiology. CBCT: Cone beam computed tomography.

In previous studies, the determination of the relationship with osteoporosis from dental panoramic radiographs was investigated by AI algorithms. In one study, 680 patients were simultaneously subjected to skeletal bone mineral density (BMD) examinations and digital panoramic radiography evaluations, and the results showed that the deep learning-based evaluation of digital panoramic radiography images could be useful and reliable in the automated screening of osteoporosis patients [18]. In another study on this subject, the effectiveness of a deep convolutional neural network (DCNN) based computer aided diagnosis (CAD) technique in osteoporosis detection on panoramic imaging was evaluated. As a result, the DCNN-based CAD technique was found to demonstrate a high level of consistency with dental radiology experts experienced in clinical osteoporosis assessment[19]. The authors suggested that a DCNN-based CAD system could provide dentists with information regarding initial diagnosis of osteoporosis and patients with asymptomatic osteoporosis may be sent to convenient medical referral for further evaluation[18,19].

In a study, a caries detection technique that used deep learning algorithms was proposed for the assessment of dental carious lesions[2]. Although the model exhibits high effectiveness in the detection of caries for both maxillary premolars and molars, this caries evaluation technique has some drawbacks. Since the study was conducted by using two dimensional images, solely interproximal and occlusal carious lesions could be detected, however; lingual and buccal carious lesions could not be detected[2].

Some of the current AI studies using cone beam computed tomography devices

Since the beginning of 2000s, cone beam computed tomography (CBCT) as a 3D imaging method has become widely used in cases where clinical examination and conventional radiographs were insufficient to reveal necessary information[20]. A CNN algorithm was created to detect periapical lesions on CBCT images. The system, which identified and enumerated teeth in volumetric data, was succeeded in diagnosing periapical lesions with 92.8% accuracy. In another study, automatic mandibular canal segmentation was performed on CBCT images with CNN developed[21]. Another area for AI is the detection of oral diseases. In a study, researchers aimed to identify and distinguish lichen planus and leukoplakia lesions with an artificial neural network trained with intraoral photographs and found promising results[22].

A 2011 study suggested that an AI technique could be useful in the automatical localization of a key landmark on CBCT images[23]. The ability to make 3D measurements for cephalometric analysis on CBCT images is an important advantage, however; the performance of automatic localization in current technique is not sufficient and effective in the clinical scenario[23]. Therefore, known techniques can be suggested for using preliminary localization of cephalometric landmarks, but manual correction is still required before further cephalometric analysis.

Limitations and future aspects

Future studies that critically assess certain issues and their clinical potential are essential. In spite of the promising performance results obtained from current AI techniques, it is mandatory to confirm the effectivenes and consistency of these techniques by using appropriate external data from new patients or collected from other dental institutions[24]. In its future goals, it can be expected not only to strengthen the effectiveness of AI techniques on par with specialists, but also to diagnose initial pathologies that are invisible to the human eye.

CONCLUSION

AI has the potential to revolutionize healthcare and dentistry. Owing to recent developments in the field of AI, scientists have become increasingly enthusiastic about conducting AI research. Image and patient recognition are important in DMFR. However, initial investment costs are currently high, and inappropriate assumptions may be made in a real-life clinical scenarios. Hitherto, DMFR-related AI studies revealed a certain degree of successful results. However, the human physiological system is exceedingly complex. As such, AI is acceptable as a supplementary method, but it cannot be seen a substitution for human knowledge, capabilities, and decision-making abilities. Additionally, the diagnostic performance of AI models may differ depending on the algorithms that are used. It is essential to validate the consistency and effectiveness of these techniques by using accurate representative images from different sources before implementing and applying these techniques to real clinical situations. With that said, further research in the field of AI has the potential to make great contributions to DMFR.

FOOTNOTES

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SYSTEMATIC REVIEWS

Immunosuppressive treatment and radiotherapy in kidney transplant patients: A systematic review

Valentina Lancellotta, Andrea D'Aviero, Bruno Fionda, Calogero Casà, Ilaria Esposito, Francesco Preziosi, Anna Acampora, Fabio Marazzi, György Kovács, Barbara Alicja Jereczek-Fossa, Alessio Giuseppe Morganti, Vincenzo Valentini, Maria Antonietta Gambacorta, Jacopo Romagnoli, Luca Tagliaferri

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Abstract

BACKGROUND

Immunosuppression (IS) therapy may contribute to cancer development. Some authors have proposed to reduce immunosuppression drugs dose in case of viral infections, in immunosuppression-related diseases, and in patients undergoing radiotherapy. The present analysis reports the results of a systematic review on kidney transplant recipients undergoing immunosuppression and radiotherapy.

AIM

To define if it is necessary reduce immunosuppression drugs during radiotherapy.

METHODS
The literature search was based on three electronic databases (Pubmed, Scopus, and Web of Science) using selected keywords linked through the "AND" and "OR" Boolean operators to build specific strings for each electronic search engine. Two researchers independently screened the citations, and disagreement was resolved by discussion or through the intervention of a third author. The review was conducted and reported according to the PRISMA statement. Extracted data were narratively synthesized, and, where possible, frequencies, percentages, and ranges were calculated.

RESULTS
The literature search resulted in 147 citations. After abstracts screening, 21 records were selected for full-text evaluation. Fifteen of these were excluded, leaving six papers considered suitable for analysis. There is still no clear evidence that withdrawing antimetabolites and/or calcineurin inhibitors and/or mammalian target of rapamycin-inhibitors, as opposed to continuing maintenance IS, improves patient survival in kidney transplant recipients with cancer undergoing radiotherapy. Only few retrospective studies on small cancer patient cohorts are available in this setting, but without comparison of different immunosuppression treatments. Even where immunosuppression therapy was described, patient survival seemed to be correlated only with cancer stage and type.

CONCLUSION
The results of this systematic review do not support the reduction of immunosuppression dose in patients undergoing radiotherapy.

Key Words: Renal transplant patients; Graft rejection; Immunosuppression; Radiotherapy; Survival

Core Tip: This systematic review aimed to define the need of immunosuppressive therapy modulation during radiotherapy. There is still no clear evidence that withdrawing antimetabolites and/or calcineurin inhibitors and/or mammalian target of rapamycin-inhibitors improves patient survival in kidney transplant recipients with cancer undergoing radiotherapy. Even where immunosuppression therapy was described, patient survival seemed to be correlated only with cancer stage and type. The results of this systematic review do not support the reduction of immunosuppression dose in patients undergoing radiotherapy.

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INTRODUCTION

Renal transplant patients have an increased risk of developing *de novo* cancers, with an incidence up to four times higher than the general population[1-3]. Recipients of transplanted organs have variable risk of cancer development. In fact, the risk of developing malignancies depends on transplanted organ, exposure to lymphocyte-depleting antibody-based therapies, immune status of the donor/recipient, and type of immunosuppressive therapy[4,5]. Current immunosuppressive regimens involved in carcinogenesis after organ transplantation are based on a combination of T-cell depleting or inhibiting agents, such as calcineurin inhibitors, monoclonal and polyclonal antibodies, cell cycle inhibitors, antimetabolites, and corticosteroids[6]. As for other oncological settings, radiotherapy (RT) may play a significant role in the treatment of cancer in transplanted patients[7]. However, RT may also have adverse effects in these patients and in particular an increased immunosuppressive effect induced by anti-rejection drugs[8,9]. This effect depends on several factors such as total dose, treatment technique, dose/fractionation, and irradiated volume. Treatment techniques are external beam RT (EBRT) or interventional RT (IRT), also known as brachytherapy[10-12].

Despite the "fragility" of transplanted kidneys, RT seems to be feasible also in this patient population [13-22]. Moreover, modern and high-precision RT techniques can deliver the dose only to the macroscopic tumor while sparing immune cells in the surrounding tissues with consequent reduction of

the suppressive effect on the immune system[23,24]. On the other hand, in kidney-transplanted patients, immunosuppressive regimens may counteracts the RT immunostimulatory effect. More generally, considering the immunosuppressive effect of RT due to bone marrow toxicity, and therefore the possible increased effect of anti-rejection drugs, a relevant problem in these patients concerns the need to modulate immunosuppressive therapy during and after RT. However, clear evidence regarding this topic is lacking in literature. Furthermore, guidelines on the management of immunosuppressive therapy in patients undergoing RT are also missing. Indeed, only a few studies have addressed this issue and literature reviews on this topic are missing. Based on this background, this systematic review aimed to define the need of immunosuppressive therapy modulation during RT.

MATERIALS AND METHODS

Development of clinical question

The clinical question was developed based on the Population, Intervention, Comparison, and Outcomes (PICO). The clinical question was: (P) In kidney transplant recipients with cancer undergoing RT, maintaining antimetabolites and/or calcineurin inhibitors and/or mammalian target of rapamycin (mTOR) inhibitors (I) is superior when compared to withdrawal of antimetabolites and/or calcineurin inhibitors and/or mTOR inhibitors (C), in relation to the outcomes (O) of benefit and harm (Table 1)? and reports the development of Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Recommendation.

Search strategy and selection of evidence

The systematic review was conducted in accordance with the PRISMA guidelines[25]. We performed a comprehensive literature search using PubMed, Scopus, and Web of Science (up to July 2019) using selected keywords linked through the Boolean operators "AND" and "OR" to build specific strings for each electronic search engine (Table 2 and Figure 1). ClinicalTrials.gov was searched for ongoing or recently completed trials, and PROSPERO was searched for ongoing or recently completed systematic reviews. Electronic search was supplemented by manually searching the references of included studies and review articles. The search was restricted to papers published in English. In order to avoid the missing of relevant studies, we chose this strategy burdened by high sensitivity and low specificity. Conference papers, surveys, letters, editorials, book chapters, case reports, and reviews were excluded. Time restriction (2010-July 2019) of the publication was considered. Studies were identified through a search process performed by three independent reviewers (LT, VL, AA), and uncertainty regarding eligibility was resolved by a multidisciplinary committee (JR-transplant surgeon, FM-radiation and medical oncology, FP-radiation oncologist, CC-radiation oncologist, IE-dermatologist). Eligible citations were retrieved for full-text review. An external expert committee defined the outcomes of benefit and harm (GK, BJF, AGM). A multidisciplinary master board (VV, MAG, LT, JR) coordinated the project and performed the final independent check and the definitive approval of the review. The GRADEpro Guideline Development Tool (McMaster University, 2015) was used to create summary of findings tables in Cochrane systematic reviews. The quality assessment showed high clinical and methodological heterogeneity and risks of bias in the included studies, making quantitative synthesis inappropriate. Therefore, meta-analysis outcomes were not reported.

Inclusion criteria

(1) Kidney transplant recipients with cancer undergoing RT; (2) Reporting patients overall survival (OS), progression free survival, graft survival, toxicity, and local control; (3) Published in English language as original articles; (4) Time restriction (2010-2019).

Exclusion criteria

Conference papers, surveys, letters, editorials, book chapters, and literature reviews.

Identification of Outcomes

The external expert committee identified the following outcomes of benefit: OS (defined as the time from baseline to death from any cause or last follow-up), graft survival (defined as time from transplant to graft failure), progression free survival (PFS, defined as time from baseline to clinical or radiological progression), and local control (LC, defined as time from baseline to cancer detected in the treated site at any time after initial treatment). The identified outcome of harm included acute and late toxicity. All these outcomes were considered as “critical” for the decision-making process.

Quality of evidence evaluation

Certainty of evidence for all selected outcomes was performed according to the GRADE approach, considering study limitations, imprecision, indirectness, inconsistency, and publication biases. Certainty level started at higher pre-specified level for randomized controlled trials, but levels of certainty could

Table 1 Population, Intervention, Comparison, and Outcomes model

PICO	
Patients	Kidney transplant recipients with cancer undergoing radiotherapy
Intervention	Withdraw antimetabolites and/or calcineurin inhibitors and/or mTOR inhibitors
Comparator	Maintain antimetabolites and/or calcineurin inhibitors and/or mTOR inhibitors
Outcome	Core outcome sets
Time frame	2010-2019
Study type	RCTs, meta-analysis of RCT; observational analytical studies

mTOR: Mammalian target of rapamycin; PICO: Population, Intervention, Comparison, and Outcomes; RCT: Randomized controlled trial.

Table 2 Search strategy

Electronic engineer	Search string
Pubmed	((“Renal transplant” OR “kidney transplant” OR “kidney transplantation” OR “renal transplantation”) AND (metastasis OR metastatic OR metastases OR “cancer” OR neoplasm OR “tumour” OR “cancers” OR “tumours” OR “tumor” OR “tumors” OR neoplasms OR melanoma OR PTLD OR lymphoma) AND (radiotherapy OR “radiation therapy”)) AND (“calcineurin inhibitors” OR “calcineurin inhibitor” OR CNI OR tacrolimus OR cyclosporine OR everolimus OR sirolimus OR “mTOR inhibitors” OR “mTOR-inhibitors” OR antimetabolites OR “antimetabolite”)
Web of Science	ALL=(((Renal transplant) OR (kidney transplant) OR (kidney transplantation) OR (renal transplantation)) AND (metastasis OR metastatic OR metastases OR cancer OR neoplasm OR tumour OR cancers OR tumours OR tumor OR tumors OR neoplasms OR melanoma OR PTLD OR lymphoma) AND (radiotherapy OR (radiation therapy)) AND ((calcineurin inhibitors) OR (calcineurin inhibitor) OR CNI OR tacrolimus OR cyclosporine OR everolimus OR sirolimus OR (mTOR inhibitors) OR (mTOR-inhibitors) OR antimetabolites OR antimetabolite))
Scopus	((“Renal transplant” OR “kidney transplant” OR “kidney transplantation” OR “renal transplantation”) AND (metastasis OR metastatic OR metastases OR “cancer” OR neoplasm OR “tumour” OR “cancers” OR “tumours” OR “tumor” OR “tumors” OR neoplasms OR melanoma OR PTLD OR lymphoma) AND (radiotherapy OR “radiation therapy”)) AND (“calcineurin inhibitors” OR “calcineurin inhibitor” OR CNI OR tacrolimus OR cyclosporine OR everolimus OR sirolimus OR “mTOR inhibitors” OR “mTOR-inhibitors” OR antimetabolites OR “antimetabolite”)AND (LIMIT-TO (PUBYEAR, 2019) OR LIMIT-TO (PUBYEAR, 2018) OR LIMIT-TO (PUBYEAR, 2017) OR LIMIT-TO (PUBYEAR, 2016) OR LIMIT-TO (PUBYEAR, 2015) OR LIMIT-TO (PUBYEAR, 2014) OR LIMIT-TO (PUBYEAR, 2013) OR LIMIT-TO (PUBYEAR, 2012) OR LIMIT-TO (PUBYEAR, 2011) OR LIMIT-TO (PUBYEAR, 2010) OR LIMIT-TO (PUBYEAR, 2009)) AND (LIMIT-TO (LANGUAGE, "English"))

CNI: Calcineurin inhibitor; mTOR: Mammalian target of rapamycin.

be downgraded if limitations in one of the above-mentioned domains were detected. Evidence was classified as having high, moderate, low, and very low level of certainty.

Benefit/harm balance and clinical recommendation

Based on the summary of evidence, the following judgments about the benefit-to-risk ratio between intervention and comparison were stated: Favorable, uncertain/favorable, uncertain, uncertain/unfavorable, and unfavorable (both for intervention or comparison). The strength of the recommendation was considered as strong positive, conditional positive, uncertain, conditional negative, or strong negative.

RESULTS

The flowchart of the study selection process is shown in Figure 1. The literature search resulted in 147 single citations. After literature screening, 21 records were identified for full-text evaluation. Out of these, 15 were excluded, and the reasons for exclusion are reported in Figure 1. Six full text papers were considered eligible and were included in the final analysis.

Characteristics of the included studies

All studies were retrospective and included a total of 65 kidney transplant patients with subsequent cancer diagnosis. Regarding the type of cancer, five studies included prostate cancer (PCa) patients while one study reported on subjects with lymphoma. No direct comparisons between different treatment approaches in terms of immunosuppressive therapy modulation was performed. The main

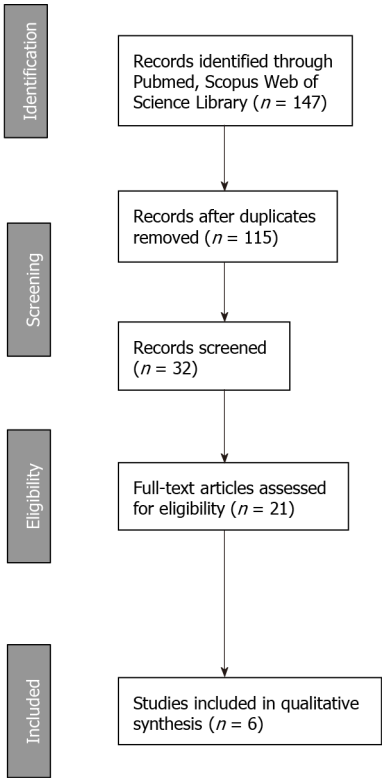

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Figure 1 PRISMA flow-chart for outcomes and toxicity.

characteristics of included studies are shown in Table 3 (first author, objective, treatment features, and main results).

Literature review

Antunes *et al*[13] analyzed the incidence of urologic malignancies in renal transplant recipients and reported on their treatment and outcomes. Twenty-nine PCa patients were included in the study with a mean age of 62.6 ± 6.1 years (range: 50-73 years). EBRT was performed in 5 patients. Although the authors did not find a statistically significant difference between type of immunosuppressive drugs and PCa development, they emphasized that 13 out of 29 patients (44.8%) received azathioprine. No statistically significant impact of duration or type of immunosuppression on *de novo* development of urologic malignancies or OS was recorded. No patient undergoing RT had allograft failure. Follow-up duration after PCa treatment ranged from 3 mo to 96 mo. One-, five-, and ten-year OS rates after PCa diagnosis were 86.2%, 86.2%, and 79.3%, respectively. Only 1 patient died of PCa. The remaining patients died of PCa-independent reasons (cardiac failure or infection)[13].

Binsaleh *et al*[15] retrospectively analyzed treatment and outcome of 9 renal transplant patients with subsequent PCa. Median age at PCa diagnosis was 63.6 years. One patient was treated with androgen deprivation therapy alone, 4 patients with RT alone, and 4 patients with a combination of androgen deprivation therapy and EBRT (60-66 Gy). Immunosuppressive therapy was as follows: 4 patients were on cyclosporine, azathioprine, and steroids regimen; 3 patients received cyclosporine, mycophenolate, and steroids (then changed to a sirolimus-based therapy); 1 patient was on tacrolimus, azathioprine, and steroids regimen; 1 patient received tacrolimus, mycophenolate mofetil, and steroids. Three out of the 9 patients had their immunosuppressive regimen changed from cyclosporine, mycophenolate, and steroids to a sirolimus-based therapy, and 6 had "judicious reductions" in their calcineurin inhibitor dosages. Four transplanted kidneys showed renal failure, and 3 out of 4 of them were treated with RT: 1 patient was on tacrolimus, azathioprine, and steroids therapy and was treated with EBRT alone (60 Gy); 1 patient was on tacrolimus, mycophenolate mofetil, and steroids and was treated with androgen deprivation therapy plus EBRT (60 Gy); 1 patient was on cyclosporine, azathioprine, and steroids and was treated with androgen deprivation plus EBRT (60 Gy); finally, 1 patient was on cyclosporine, azathioprine, and steroids and was treated with androgen deprivation therapy alone. The authors concluded that a combination of RT with androgen deprivation therapy provides good control of the disease while preserving renal function. The comparative long-term follow-up of patients with reduced doses of calcineurin-inhibitor-based immunosuppression or sirolimus-based treatments is not known [15].

Table 3 Characteristics of included studies

Ref.	Study design	Patients (*n*)	Mean age	Type of cancer	Intervention	Patient survival	Graft survival
Binsaleh *et al*[15], 2011	Retrospective	9	55 (range: 40-72)	PCa	RT (60-66 Gy); 3 patients had their immunosuppressive regimen changed to a sirolimus-based therapy, while 6 had "judicious" reductions of CNI dosages	NR	4/9 failure; 5/9 good
Pettenati *et al*[20], 2016	Retrospective	6	63.5 yr (± 7.2)	PCa	RT (EBRT: 76 Gy; IRT: 145 Gy) +Immunosuppressive therapy [2 pts: CNI + AZA + steroids; 19 pts: CNI + MMF + Steroids; 2 pts: MMF, mTORI + Steroids]	1 patient died of PCa	No graft loss nor change in renal function due to PCa treatment
Antunes *et al*[13], 2018	Retrospective	29	53.4 (±10,7)	PCa	RT in 5 patients (details not reported)	1-yr: 86.2%5-yr: 86.2%10-yr: 79.3%	No patient undergoing RT had allograft failure
Oh *et al* [26], 2019	Retrospective	13	66 (range: 42-80)	PCa	RT (EBRT: 78 Gy; IRT: 144 Gy) + Immunosuppressive therapy [CIA (*n* = 8), MMF (*n* = 13), AZA (*n* = 3), tacrolimus (*n* = 12), sirolimus (*n* = 9), and/or prednisone (*n* = 20)]	3 yr: 93.8%	NR
Tasaki *et al* [21], 2019	Retrospective	3	65 (range: 60-67)	PCa	RT (IRT: 145 Gy) + Immunosuppressive therapy [2 pts: CIA + MMF + MP; 1 pt: tacrolimus + MMF +MP]	NR	2 pts good graft function; 1 pt declined graft function after 2 yr
Velvet *et al* [27], 2019	Retrospective	3	59.5	Lymphoma	RT (details not reported) + reduced immunosuppressive regimen	6 mo: 66.6%	NR

CNI: Calcineurin inhibitor; mTOR: Mammalian target of rapamycin; NR: Not reported; PCa: Prostate cancer; RT: Radiotherapy; EBRT: External beam RT; IRT: Interventional RT.

Pettenati *et al*[20] published the results of their retrospective single center study. A control population of non-organ transplant and non-end-stage renal disease patients with PCa was used to compare tumor features and oncological outcome with 24 renal-transplanted patients (PCa incidence in all patients was 1.5%). Mean follow-up was 47 mo. PCa was mostly localized (*n* = 21, 87.5%) and treated with radical prostatectomy (*n* = 16, 76.2%), LDR-IRT (*n* = 3, 14.3%, 145 Gy), EBRT (*n* = 1, 4.7%), or active surveillance (*n* = 1, 4.7%). On the contrary, 3 patients had locally advanced PCa and were treated with EBRT combined with androgen deprivation therapy. Two patients were on a regimen of calcineurin inhibitors plus azathioprine plus steroids; 19 patients were on calcineurin inhibitors plus mycophenolate mofetil plus steroids; 2 patients were on mycophenolate mofetil plus mTOR inhibitors plus steroids. No graft failure due to PCa treatment was reported. Nineteen renal-transplant patients with localized PCa (90.5%) were free from biochemical recurrence at last follow-up. Considering the radical prostatectomy subset, no difference in PCa characteristics at diagnosis and biochemical recurrence rate was found between renal-transplant patients (*n* = 16) and control patients (*n* = 64). The authors concluded that localized PCa following renal transplantation was not associated with adverse features as compared to non-transplant patients. Standard treatments could be proposed to renal-transplanted patients with satisfying results both on oncological outcome and graft function[20].

Tasaki *et al*[21] retrospectively analyzed safety and efficacy of IRT in 3 patients with PCa after renal transplantation. The clinical stage was cT1N0M0 in all patients. The median age at diagnosis was 65 years (range: 60-67 years). Immunosuppressive regimens were cyclosporine A plus mycophenolate mofetil plus methylprednisolone in 2 patients and tacrolimus plus mycophenolate mofetil plus methylprednisolone in 1 patient. The median time between transplantation and IRT was 7 years (range: 4-10 years). Two patients received low dose-rate IRT (dose, 145 Gy), and one patient was treated with high dose-rate IRT (dose, 19 Gy in 2 fractions) combined with external beam irradiation (EBRT, 39 Gy in 13 fractions). Median follow-up after IRT was 44 mo (range: 34-50 mo). No patient developed biochemical or clinical progression and no clinically significant RT-induced adverse events were reported. Two patients maintained a good graft function while one patient had a decline of graft function 2 years after IRT. The authors concluded that low dose-rate IRT and high dose-rate IRT of PCa seem feasible and safe in renal-transplanted recipient with oncological outcomes similar to those recorded in the general population[21].

Oh *et al*[26] reported on biochemical disease-free survival, distant metastasis free, OS, and toxicity in 28 patients with renal transplant who were subsequently treated with definitive RT for PCa. The median age was 66 years, and median follow-up time was 30 mo. Twenty-four patients (86%) were treated with IRT (144 Gy), and 4 patients (14%) were treated with external-beam RT (78 Gy). Immunosuppressive regimens were cyclosporine (*n* = 8), mycophenolate mofetil (*n* = 13), azathioprine (*n* = 3), tacrolimus (*n* = 12), sirolimus (*n* = 9), and/or prednisone (*n* = 20). At last follow-up, 2 patients had died, 1 from

metastatic PCa and 1 from other reasons. Three-year biochemical relapse-free survival, distant metastasis-free, and OS were 95.8%, 93.1%, and 93.8%, respectively. One patient developed grade 3 gastrointestinal late toxicity. The authors concluded that organ transplant recipient with PCa and treated with RT have excellent 3-year outcomes[26].

Velvet *et al*[27] conducted a single center retrospective study on management and outcomes of central nervous system lymphomas in 6 kidney transplant patients. During the lymphoma treatment, immunosuppressive therapy was reduced in all patients. Mycophenolate mofetil and prednisolone without calcineurin inhibitor were prescribed to 5 out of 6 patients. Three out of six patients underwent RT: one patient was also treated with chemotherapy and four cycles of cytotoxic T lymphocytes (alive at last follow-up); one patient was also treated with craniotomy and rituximab (graft failure and then death for acute left ventricular failure); one patient was also treated with chemotherapy (unknown cause of death). RT total dose and technique were not reported and 6-mo OS was 66.6%. This study supports observational data suggesting that patients treated with mycophenolate mofetil and without calcineurin inhibitor may have increased risk of cancer after transplantation[27].

Data synthesis

No study showed that withdrawing antimetabolites and/or calcineurin inhibitor and/or mammalian target of rapamycin-inhibitors as opposed to continuing maintenance immunosuppression improves patient survival in kidney transplant recipients with cancer undergoing RT.

DISCUSSION

The present systematic review showed that in kidney transplant recipients developing cancer and undergoing RT, clear evidence on improved function of the graft and/or of patients survival after modulating or withdrawing immunosuppressive therapy, as opposed to continuing maintenance immunosuppression, is lacking; conversely, only few retrospective studies on small RT-treated cancer cohorts are available, mainly including PCa patients, without comparison between different immunosuppressive strategies[26,27]. RT appears to be a feasible therapeutic option also in this setting, with oncological outcomes not clearly different from the general patient population[28].

In fact, while no studies compared different immunosuppressive treatments, when immunosuppressive drugs were reported, patients' survival seemed to be correlated only with cancer stage or type. Due to lack of evidence, it seems reasonable to entrust the clinical management of these patients to a multi-disciplinary team including nephrologists, cancer surgeons, medical and radiation oncologists, pathologists, and radiologists. In fact, discussion of clinical cases in a multidisciplinary expert team could allow a more homogeneous treatment approach and improvement of clinical outcomes. This evaluation needs to consider the clinical specificities beyond tumor burden, such as comorbidities, compliance to treatment, general performance status, and history of the disease to select the best approach for the individual patient following the principles of personalized medicine. Furthermore, for clinical and deontological reasons, it is also mandatory to discuss all possible implications with the patient to define the therapeutic strategy and obtain a detailed informed consent.

Moreover, due to the lack of available results from prospective trials, studies with this design should be promoted. However, considering the rarity of patients undergoing renal transplantation and requiring RT, and therefore the difficulty in carrying out prospective trials, an alternative aimed at generating evidence in this field could be to share retrospective data from different centers in order to create pooled analyses[29,30].

This study has several limitations. Only six studies were included in the analysis, totaling only 65 patients. Furthermore, all studies have been lacking in reporting important data such as details of RT, radiation-induced toxicity, a complete assessment of renal function, and the impact of RT on immune function. These limitations prevent clear conclusions from being drawn on the question of this review and, in particular, on the need to suspend or modulate immunosuppressive therapy in patients undergoing renal transplantation and subsequent RT.

CONCLUSION

There is no evidence that immunosuppressive therapy should be modulated in kidney transplant patients undergoing RT. Prospective studies or pooled analyses are needed to define the proper treatment for this very selected group of patients.

ARTICLE HIGHLIGHTS

Research background

Cancer is the second most common cause of mortality and morbidity in kidney transplant recipients. Immunosuppression can influence the efficacy of cancer treatment and modification of the immunosuppressive regimen may restore anti-neoplastic immune responses improving oncologic prognosis. However, patients are usually reluctant to modify their immunosuppression, fearing rejection and potential graft loss.

Research motivation

To develop reference points for guiding the transplant professionals in the clinical decision-making process and to improve the management of kidney transplant recipients with cancer.

Research objectives

Little evidence is available on radiotherapy management of cancer in kidney transplant recipients; in certain instances (*e.g.*, in case of pelvic cancer or cancer of the transplanted kidney) it is also unclear which could be the best loco-regional treatment option, among the full range of ablative devices/techniques, to be used as an alternative to nephron sparing surgery, currently the preferred option.

Research methods

The overall process included: (1) The formulation of one specific question based on the Population, Intervention, Comparison, and Outcomes methodology; (2) Systematic literature review and summary for experts for each question; and (3) Extracted data were narratively synthesized and, where possible, frequencies, percentages, and ranges were calculated.

Research results

There is still no clear evidence that withdrawing anti-metabolites and/or calcineurin inhibitor and/or mammalian target of rapamycin inhibitors as opposed to continuing maintenance immunosuppression might improve patient survival in kidney transplant recipients with cancer undergoing radiotherapy. There are few retrospective studies on small cancer cohorts undergoing radiotherapy, especially prostate, without comparison of different immunosuppressive treatments. The radiation therapy can be performed with excellent oncological outcomes. No studies have compared different immunosuppressive treatment, and, when the immunosuppressive drugs are reported, patients' survival seems to be correlated only with cancer stage or type. In addition, there are no data on the eventual effects of immunosuppressive drugs, especially mammalian target of rapamycin inhibitors, on the healing of radiotherapy-induced skin toxicity.

Research conclusions

Although all the statements of the consensus are not methodologically evidence-based and their strength might therefore be questionable, they represent a starting point to orient transplant physicians in their everyday practice, and, above all, these statements clearly indicate the points that need to be addressed in the clinical research in this setting.

Research perspectives

Prospective studies or pooled analyses are needed to define the proper treatment for this very selected group of patients.

FOOTNOTES

Author contributions: Valentini V, Morganti AG, Tagliaferri L, and Romagnoli J contributed to scientific committee; Acampora A, Lancellotta V, and Tagliaferri L contributed to working group performing literature review and summary for experts; Romagnoli J, Marazzi F, Preziosi F, Casà C, and Esposito I contributed to resolve uncertainty regarding eligibility; Kovács G, Jereczek-Fossa A, and Gambacorta MA contributed to revise the manuscript.

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